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DISEASES of CHILDREN

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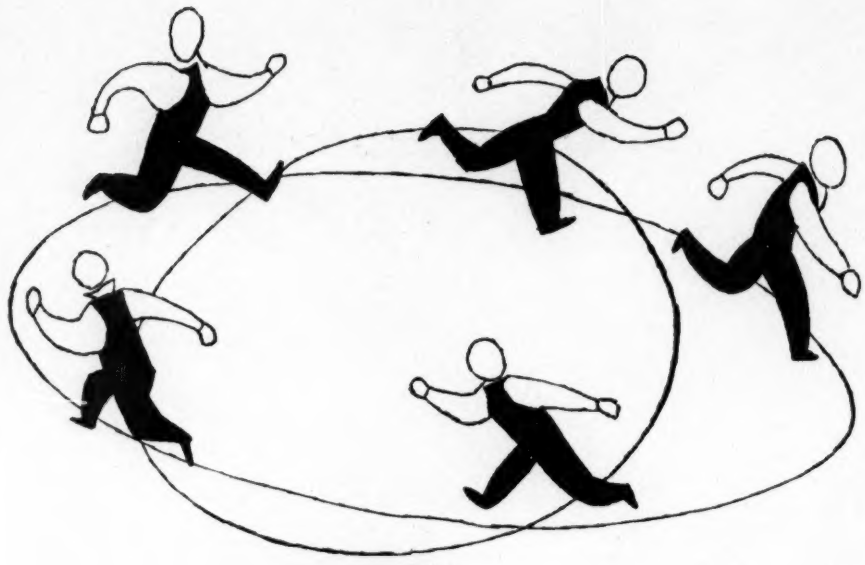

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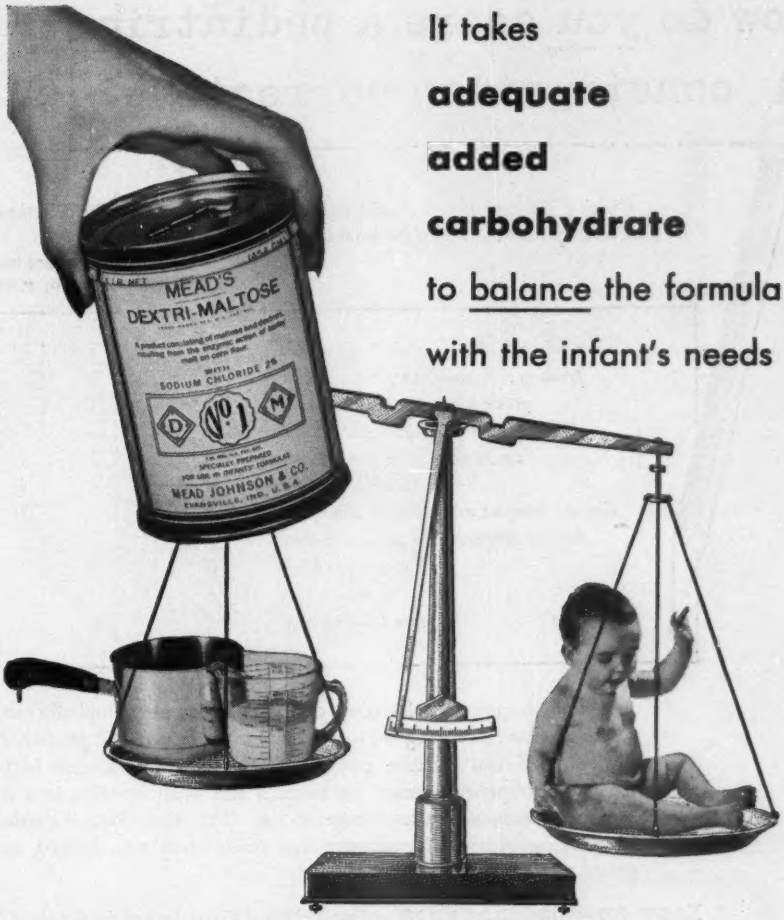

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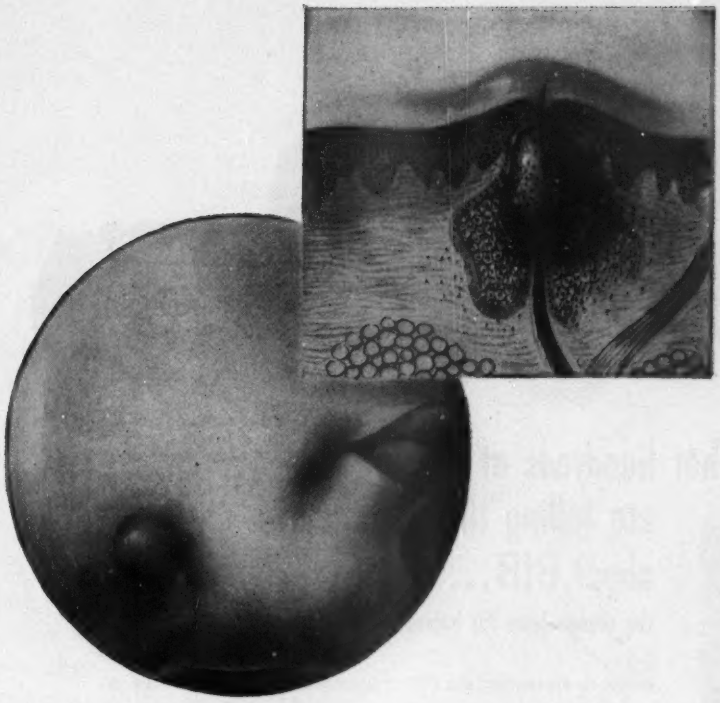

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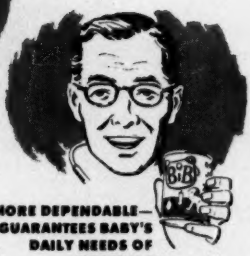

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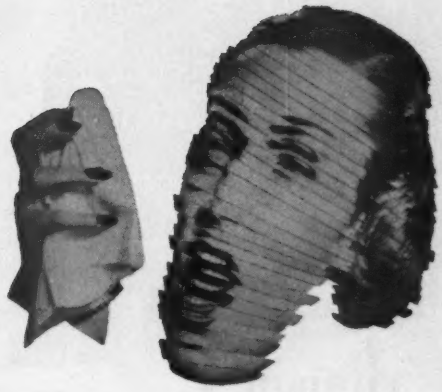

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1. Lewis, J. M., et al.: Jl. Pediatrics 31:496, 1947
2. Kramer, B., et al.: Am. Jl. Dis. Child. 73:543, 1947
3. Halpern, G. R., et al.: Science 106:40, 1947
4. Nutrition Reviews 5:286, 1947
5. Clifford, S. H. and Weller, K. H.: Pediatrics 1:505, 1948
6. Popper, H., et al.: Gastroenterology 10:987, 1948
7. Davidson, D. M., et al.: Jl. Invest. Derm. 12:221, 1949
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*Hill, L. W.: New England J. Med. 242:288, 1950

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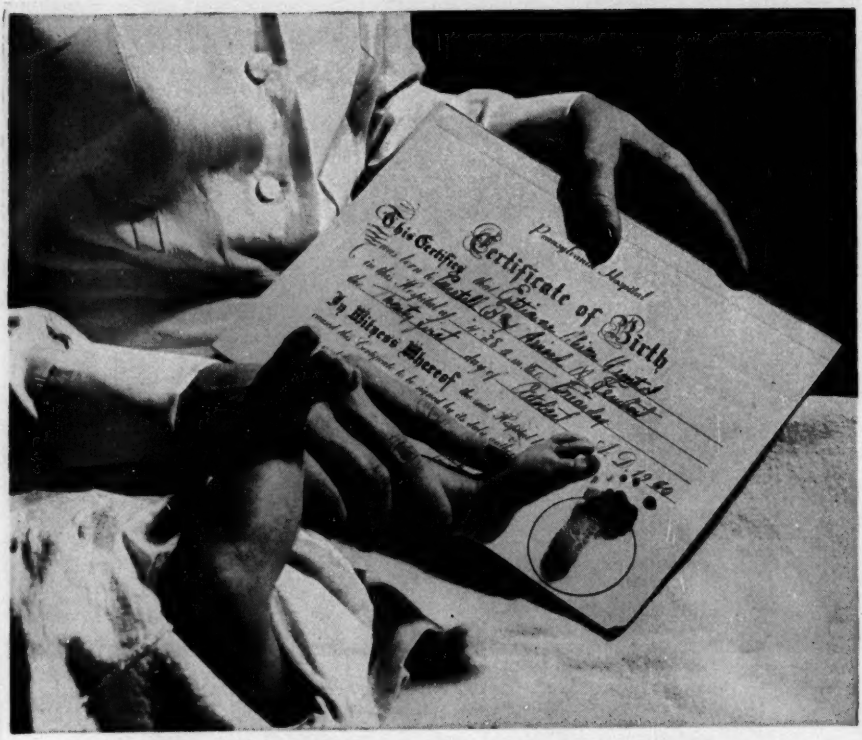

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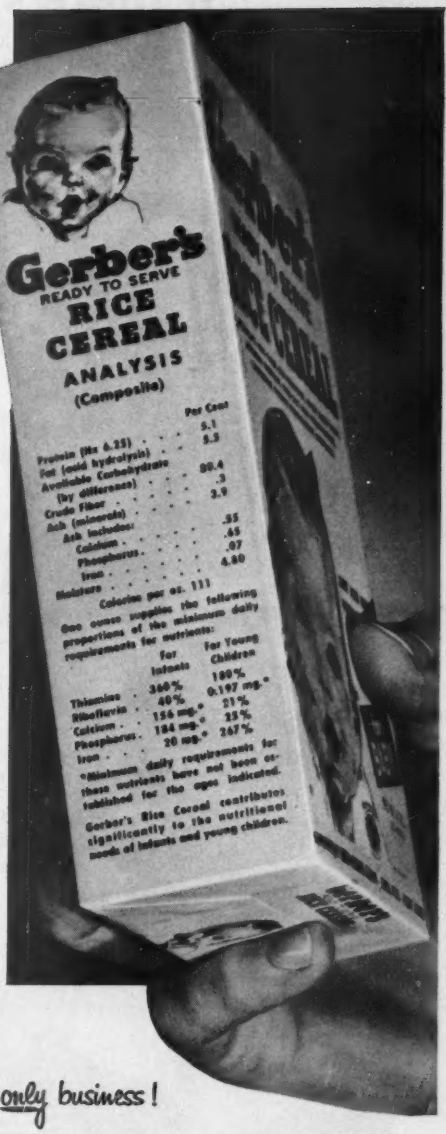
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VOLUME 82 SEPTEMBER 1951 NUMBER 3

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PLACE AND VALUE OF SUMMER CAMPS IN MANAGEMENT OF JUVENILE DIABETES

Observations and a Report of Activities at a Camp for Diabetic Boys in 1950

JOHN W. STEPHENS, M.D.
AND
ALEXANDER MARBLE, M.D.
BOSTON

IT IS NOW well over 25 yr. since the first summer camp for diabetic children was established by Dr. Leonard F. C. Wendt of Detroit. The first camp to have continuous operation (except for the war years) is Camp Ho Mita Koda, founded in 1929 by Dr. Henry John[1] of Cleveland. Three years later the Clara Barton Birthplace Camp for diabetic girls was established at North Oxford, Mass. During the summer of 1950, in its 19th consecutive year of operation, 119 diabetic girls were accommodated for periods of from two to eight weeks each. There was in addition a two-week supplementary period for older young women which allowed 43 patients the advantages of a vacation.

Despite this long history which began shortly after the introduction of insulin into general use and despite the success which has attended efforts expended in such summer camps, their place and value in the treatment of diabetes in childhood and adolescence are not fully appreciated. Even today there are only 15 camps in the United States and Canada. These are the following: Camp Firefly, Spring Mount, Pa.; Washington Camp, Rockville, Md.; Camp Nyda, Burlingham, N. Y.; Clara Barton Birthplace Camp (girls), North Oxford, Mass.; Elliott P. Joslin Camp (boys), Charlton, Mass.; Priscilla White Camp (girls) and Camp Banting (boys), Seattle; Camp Whitaker, Badger, Calif.; Sweeney Camp, Gainesville, Texas; Camp Kno-Koma, Alum Creek, W. Va.; Holiday Home Camp, Lake Geneva, Wis.; Illahee Lodge, Cobourg, Ont.; Seale Harris Camp, Mobile, Ala.; Camp Ho Mita Koda, Novelty, Ohio, and two newly established camps, one at Lake Olcott, Napoleon, Mich., and one the Springdale Camp, in Nebraska. The purpose of this paper is to point out the advantages of summer camps for diabetic children. As a background for doing so, experiences during the summer of 1950 at the Elliott P. Joslin Camp for diabetic boys in Charlton, Mass., will be presented.

GENERAL INFORMATION AND PROCEDURE AT THE ELLIOTT P. JOSLIN CAMP

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1. John, H. J.: The Planning of a Camp for Diabetic Children, Am. J. Med. **1**:642-648, 1946.

erected and the camp first operated in 1948. By 1950 the buildings included a dining and recreation hall, administration building, laboratory and latrine building, seven cabins, each housing eight campers, infirmary and nurses' quarters, a physician's cabin, two cabins for other personnel, and an outdoor chapel. In addition, in older buildings already on the farmsite are a craft shop and quarters for caretakers and other personnel. The land was bought, the buildings erected, and the camp operated by funds secured from donations from the general public. The camp is leased by the Diabetic Fund (administered by the Boston Safe Deposit and Trust Co.) for a nominal sum to the Association of Universalist Women, which operates the camp. Prominent among the donors, in addition to the Association of Universalist Women, has been the Massachusetts Committee on Social Service of Unitarian Women. Experience has shown that over the years about half of the expense of operating the camp is met by fees from campers and the other half from the church sources named, the Diabetic Fund, and other donors.

Personnel.—Personnel during the summer of 1950 included a representative of the Association of Universalist Women who exercised general supervision over this camp and the Clara Barton Birthplace Camp 3 miles (5 km.) away. The direction of the Elliott P. Joslin Camp itself was in the hands of a camp director, who was responsible for the selection of the 12 counselors and seven counselors-in-training (some of the latter were older diabetic boys). The group of counselors was made up chiefly of college men with special training and skill in swimming, land sports, arts and crafts, music, nature study, and so on. A theological student and his wife lived in the cabin which housed the eight campers aged 5 and 6 yr. Other nonmedical personnel included a clerk, a cook, and two kitchen helpers. Medical personnel were chosen with the advice of the medical sponsors of the camp and included one resident physician, three graduate nurses, one dietitian, and three medical students who served as laboratory technicians.

The camp season ran for three sessions of three weeks each. The plan was that practically all campers should stay for only three weeks, and this was in general adhered to, but if space was available, certain campers were allowed to stay six or even nine weeks. The camp is run as a nonprofit organization, and no charge is made for medical care. The average cost for a camper for one week during the summer of 1950 was approximately $47.50. Campers are invited to pay any amount that they can. They are received from any source and are referred back to their home physicians or outpatient clinics at the end of the camp season.

Medical Program.—All diets were prescribed by the resident physician, and all food was weighed. Weighing was carried out at the table by the counselors. Precautions were taken to assure that there was no other source of food than that provided at meals or between-meal lunches. The purchase and preparation of food and calculation of diets were under the supervision of the resident dietitian.

The insulin dose was prescribed daily by the resident physician and administered by the nurses. Those campers who did not know how to take their insulin were instructed in its use.

The entire amount of urine voided during the 24 hr. was collected daily in large bottles marked so that the volume could be read in cubic centimeters directly from the side of the bottle. Each morning a specimen of this was tested for diacetic acid or acetone and for sugar. The tests for sugar were carried out according to the

Exton modification [2] of the Sumner method, by which the percentage of sugar is easily obtained and the total number of grams of sugar excreted daily may be calculated. In addition, single specimens of urine were tested for sugar at 7:15 a. m., 11:15 a. m., 4:45 p. m., and 7:45 p. m. These data as well as those for the carbohydrate, protein, fat, and calories in the diet and those for blood sugar and insulin dosages were recorded daily on charts especially designed for such tabulations. Blood for the determination of sugar content was obtained by puncture of the finger tip or ear lobe and the determination carried out by the Folin-Malmros method.[3] Such capillary blood sugar tests were done on each camper on two days weekly before each of the three meals and at 8:00 p. m. Ample facilities for these determinations and for the general analysis of urine and for certain other blood tests were available in a well-equipped laboratory.

Camp Routine.—The camp director was responsible for the planning and carrying out of the camp activities, with the advice of the resident physician. Although there was of necessity some rigidity in the schedule, the campers were allowed in so far as possible to select the type of activity which they desired. The program included both active and relatively inactive periods both in the forenoon and in the afternoon. All campers were required to engage in swimming and in land sports, including softball, track, volleyball, and archery. All campers had a "cook-out" once weekly in which the campers themselves went into the woods and cooked portions of their supper over open fires. These were popular, as were also the overnight camp-outs arranged twice during each three-week period. The arts and crafts shop provided recreation and exercise for days of inclement weather. Evenings were taken up by music, plays, sound movies, and such "Indian Council" activities as tribal contests around open fires.

CAMP EXPERIENCE DURING SUMMER OF 1950

Experiences during the first season of operation of the Elliott P. Joslin Camp have been described previously.[4] The results of the camp in the summer of 1950 did not differ greatly, but the whole experience emphasized the value of such projects. Consequently it is of significance to review the important data.

During the camp season of 1950, 138 boys attended. Only slightly more than one-half of these, 71, came from Massachusetts. Fourteen campers came from New York and 14 from Connecticut. Eight were from Maine, seven from Virginia, five from New Jersey, and four each from Vermont and Rhode Island. Three campers came from New Hampshire, two from Ohio, two from Pennsylvania, and one each from North Carolina, Georgia, District of Columbia, and the Philippine Islands. Of this group, however, only 135 remained their allotted times, since three of the campers returned home after two to four days because of homesickness. The ages ranged from 5 to 16.9 yr. Those 16 or older were in the counselor-in-training group. The ages of the campers arranged in five groups together with data regarding heredity and duration of diabetes are given in Table 1. It will be noted that 75 of the

2. Exton, W. G.: Diabetes and Bright's Disease as Selection Problems, Proceedings of the 28th Annual Meeting, Medical Section, American Life Convention, June, 1938.

3. Folin, O., and Malmros, H.: An Improved Form of Folin's Method for Blood Sugar Determinations, J. Biol. Chem. **83**:115-120, 1929.

4. Gabriele, A. J., and Marble, A.: Experiences with 116 Juvenile Campers in a New Summer Camp for Diabetic Boys, Am. J. M. Sc. **218**:161-171, 1949.

138 campers gave a history of diabetes in relatives, thus making an unusually high incidence of 54%. The duration of diabetes varied from 0.4 to 13.1 yr.; the average duration among the five age groups is shown in Table 1.

Diet.—Without exception all campers had been on treatment regimens which included a restricted diet. However, in most instances adherence to diet had been far from strict; consequently, any statement as to the diet followed at home prior to admission to camp would be grossly inaccurate. On arrival, the camper was usually placed on the diet prescribed for home use. During the first few days adjustments were made in the dietary prescription according to the outcome of blood and urine tests, the camper's desires, body weight, and other considerations. One general guiding principle was that the carbohydrate in the diet should usually not exceed 200 gm. daily and rarely exceed 225 gm. daily. The amount of protein averaged about 2.5 to 3.5 gm. per kilogram of body weight. As may be noted in Table 2, the diets provided on the average from 85 to 130 gm. of protein a day. The amount

TABLE 1.—*Distribution of Campers by Age Groups Showing Incidence of Heredity and Duration of Diabetes*

Age Groups, Yr.	No. of Campers	Known Heredity	Duration of Diabetes, Yr.
5- 7.9	19	10	3.4
8- 9.9	22	13	3.1
10-11.9	37	22	4.0
12-13.9	32	17	5.1
14-16.9	25	13	5.2
Total	135	75	...

TABLE 2.—*Diets Employed Shown by Averages for Five Age Groups*

Age Groups, Yr.	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories
5- 7.9	183	85	91	1,891
8- 9.9	199	99	99	2,093
10-11.9	210	103	103	2,179
12-13.9	222	118	118	2,422
14-16.9	223	130	129	2,573

of fat was gauged according to the body weight of the camper; the average values for this component of the diet varied in the five age groups from 91 to 129 gm. a day (Table 2). The result was that the diet provided for an average of from 1,891 to 2,573 Cal. a day.

Insulin.—Prior to the camp season the types of insulins received by the campers at home varied. Some were using protamine zinc insulin alone. Others had been taking crystalline and protamine zinc insulin either by separate injection or in mixtures. A few had been taking globin insulin. Two campers had received only crystalline insulin. Some had been taking NPH insulin and others a mixture of the crystalline and NPH varieties.

During the camp season a relatively wide variety of insulin programs was used. The greatest single change in insulin treatment was the shifting of a considerable number of campers to the NPH variety [5] either alone or mixed with crystalline

5. Furnished by Eli Lilly and Company, P. O. Box 618, Indianapolis, as NPH-50 insulin for investigational use.

insulin. A detailed statement regarding the various programs would not be profitable, but it is of interest that at discharge NPH insulin alone was prescribed for 53 campers, a mixture of crystalline and NPH insulin for 46 campers, and crystalline insulin plus protamine zinc insulin by separate injection for 30 others. Three campers were discharged on globin insulin, two on mixtures of protamine zinc insulin and crystalline insulins, and one on protamine zinc insulin alone.

The experience confirmed the impression previously reported that in many campers a single injection of NPH insulin daily will provide as good control of the diabetes as the giving of crystalline and protamine zinc insulins by separate injections.[6] This was found to be true particularly in those campers for whom the ratio of crystalline to protamine zinc insulin had been 1 : 3 or less. In general, when the proportion of crystalline to protamine zinc insulin had exceeded this, and particularly in those campers for whom the ratio was in the neighborhood of 1 : 2, the addition of a small amount of crystalline insulin to the NPH variety in the syringe usually was necessary in order to bring about the desired degree of control. Studies were carried out which indicated that such mixtures can be made with the preservation of most of the rapid action of the added crystalline insulin.[7]

TABLE 3.—*Degree of Control of Diabetes on Three Insulin Programs*

Insulin Program *	Total No. Camper Days	Percentage of Camper Days in Which Were Found Amounts of Glycosuria Listed			
		0 to 2.0 Gm. Glucose/ 24 Hr.	2.1 to 5.0 Gm. Glucose/ 24 Hr.	5.1 to 10.0 Gm. Glucose/ 24 Hr.	10.1 or More Gm. Glucose/ 24 Hr.
NPH-50	1,397	34.3	16.5	18.1	31.1
Cr.-NPH-50	1,296	29.2	13.6	20.0	37.2
Cr.-p. z. separately	858	37.4	10.4	17.6	34.6
Cr.-p. z. mixed	42 †	0	16.7	33.3	50.0
P. z.	21 †	0	0	66.7	33.3
Gl.	42 †	50.0	0	14.3	35.7

* Cr. indicates crystalline insulin; p. z., protamine zinc insulin; Gl., globin insulin.
† Figures are too small to serve as the basis for conclusions.

In Table 3 are charted the results obtained with the various insulin programs according to the number of grams of sugar excreted in the urine per 24 hr. The number of camper days on each insulin program is recorded. It is evident that with the three regimens used most there was no significant difference in the results. It must be noted that mixtures of crystalline and NPH insulins were used for those campers for whom the injection of NPH insulin alone was not satisfactory. Keeping in mind the degree of severity and instability of diabetes of patients in these age groups, it is remarkable that it was possible to achieve control to the extent that in 29 to 37% of camper days less than 2 gm. of sugar appeared in the urine. It will be recalled that the diets contained in general from about 180 to 225 gm. of carbohydrate a day, so that an excretion of 2 gm. or less represented about 1% of the carbohydrate and of course a considerably smaller percentage of the total available glucose.

6. Gabriele, A. J., and Marble, A.: Clinical Experience with a New Modified Protamine Insulin (NPH-50), Am. J. Digest. Dis. **16**:197-206, 1948.

7. Stephens, J. W.; Donaldson, R. M., Jr., and Marble, A.: The Use of Mixtures of NPH and Unmodified Insulin, A. M. A. Arch. Int. Med., to be published.

Insulin Reactions.—It is not surprising that hypoglycemic attacks occurred on each type of insulin program which was used. In looking over the data it is not possible to say that reactions were any commoner on one insulin program than another. Although the tabulation brings out that there were a total of 1,502 reactions in 3,672 camper days in the summer of 1950, this figure errs on the side of being too large, since the majority of "reactions" were treated and reported by counselors. In order to prevent delay in treatment, counselors were allowed to give small amounts of carbohydrate (a glucose wafer furnishing 2 gm. of glucose or 50 cc. of ginger ale furnishing 5 gm.) when a camper complained of weakness or other symptoms which seemed genuine and most likely due to a low blood sugar. Although the counselors on the whole showed good judgment, undoubtedly many episodes in which the blood sugar was not at a truly hypoglycemic level were reported as insulin reactions. As an index of this may be taken the fact that during the whole summer there were listed by the physician and nurses only 13 severe reactions. In only two instances was it necessary to give dextrose intravenously, and in only nine others was epinephrine given.

TABLE 4.—*Weights and Heights of Diabetic Boys as Compared with Those of Nondiabetic Boys of Comparable Ages**

Age Groups, Yr.	No.	Net Weight, Lb.		Net Height, In.	
		Normal	Campers	Normal	Campers
5- 5.9	4	35.1- 43.5	49.0	41.2-44.2	45.1
6- 6.9	6	39.2- 48.6	52.0	43.5-46.5	45.9
7- 7.9	6	43.0- 53.2	63.0	45.6-48.8	50.3
8- 8.9	10	47.2- 58.4	63.0	47.5-50.9	52.4
9- 9.9	9	51.6- 64.4	66.0	49.5-52.9	53.6
10-10.9	13	57.0- 71.6	77.0	51.4-55.0	55.5
11-11.9	18	63.0- 79.4	79.0	53.3-57.1	56.8
12-12.9	14	69.4- 87.2	90.0	55.2-59.0	58.8
13-13.9	18	75.9- 95.7	99.0	56.9-60.9	60.9
14-14.9	11	81.1-102.9	110.0	58.6-62.8	63.3
15-15.9	10	89.4-113.4	112.0	60.3-64.5	64.7
16-16.9	4	96.0-122.0	129.0	61.8-66.2	67.0

* Normal values are taken from Engelbach, W.: Endocrine Medicine, Springfield, Ill., Charles C Thomas, Publisher, 1932, pp. 304-305.

Physical Findings.—On admission and at discharge a complete physical examination was made and the findings recorded. In addition, certain special studies were carried out, the results of which will be presented. In Table 4 are given the heights and weights of the campers arranged according to age for comparison with those of nondiabetic children of comparable ages. It is obvious that in every age group the diabetic children were taller and heavier than those in the normal groups.

In only two instances was there significant enlargement of the liver, but in no camper could the spleen be felt. Eighty-nine of the children received funduscopic examinations by a certified ophthalmologist, and of these, 83 were regarded as entirely normal. Of the six campers with abnormalities, two showed lens opacities, one had congenital cataracts, one had exudatelike spots in the macular region, possibly congenital, and two showed aneurysmal dilatations of veins. In no camper were there definite hemorrhages or exudates.

Tests of capillary fragility were carried out by pressure of a blood-pressure cuff at a level of 80 mm. for four minutes and by counting the number of petechiae in a circle 6 cm. in diameter drawn on the volar surface of the forearm below the

antecubital space. In only one camper could the result be considered abnormal (in this case there were over 20 petechiae). Only four other campers showed petechiae; one had 14, and in the others there were less than 10, which was considered within normal limits.

Laboratory Studies.—Only one camper gave as much as a 1+ reaction for albumin, and four others showed only a trace. The range of hemoglobin level in 109 campers tested was 11.3 to 15.0 gm., with an average of 12.7 gm. per 100 cc. The blood cholesterol level ranged from 125 to 258 mg. in 52 campers so studied, with an average of 173 mg. per 100 cc. Thirteen of the 52 campers had a cholesterol value of over 200, and five had one below 140 mg. per 100 cc. These 52 campers had studies made of the total protein, albumin, and globulin content of the blood serum. Total protein values ranged from 6.05 to 7.40 gm. per 100 cc., with an average of 6.49 gm. Serum albumin varied from 4.11 to 5.03 gm., with an average of 4.56 gm. per 100 cc. Serum globulin ranged from 1.18 to 2.43 gm., with an average of 1.93 gm. per 100 cc.

Roentgenography of the chest was carried out in nine campers who had had diabetes for 10 or more years, and in each instance the results were normal. Furthermore, in these nine campers roentgenograms were taken of the aorta (lateral view), pelvis, and legs from knee to ankle; in no instance was calcification seen in the arteries.

Clinical Features.—Of 118 campers for whom data were available, 19, or 16%, had had diabetic coma one or more times. Of this number, five had had coma more than once. Two campers were subject to epilepsy and were under treatment for it.

Behavior Problems.—It is generally recognized that psychological problems are commoner in diabetic than in nondiabetic children. There is ample reason for this when one considers the restrictions as regards diet, the inconvenience and possible pain of insulin injections, the relative rigidity of the diabetic life with the necessity for urine and blood tests, and the natural dislike of the child to be different from his fellows. Added to this is often the factor that not infrequently children are harmed because of overindulgence and protection on the part of parents. These psychological traumas are augmented if the camper has experienced serious complications from time to time, such as bouts of severe acidosis or frequent insulin reactions. It is no wonder therefore that in a group of diabetic children at a summer camp one encounters various behavior problems. Of the 80 boys seen during the last six weeks of camp about whom special notations were made 20, or one-fourth, presented problems of one type or another. Perhaps the commonest difficulty was that concerned with an antagonistic and resentful attitude, with resistance to camp authority and camp discipline. This was often associated with a tendency to break diet if the opportunity was presented. It was noteworthy that campers in this group were those who during insulin reactions were the most active and difficult to handle. At least three boys had severe temper tantrums; one of these was subject to attacks of petit mal. Two campers had a weakness for stealing. Others showed introversion and abnormaly quiet attitudes.

It is evident from the above that much could and should be done in the way of psychiatric assistance, particularly at the level of child guidance and the management of behavior problems.

COMMENT

The experience in the Elliott P. Joslin Camp during three summers and at the nearby Clara Barton Birthplace Camp for 19 summers has shown forcibly the need and value of such camps. In the present day when hospitals are overcrowded and accommodations expensive, it is not possible or profitable to bring otherwise healthy children with diabetes into a hospital for study and treatment, except perhaps for initiation of therapy and because of specific complications. Nevertheless, such children need periodic examinations and studies of a nature more thorough and revealing than is possible at single visits to the doctor's office or the outpatient clinic. Furthermore, they need an opportunity to acquire instruction in diabetes and its complications and to be taught self-reliance. They should have an opportunity to enjoy life in a summer camp just as their nondiabetic brothers and sisters do. They should have the opportunity to associate with other diabetics of their own ages so that they will overcome the feeling of loneliness which often is a problem.

Estimates as to the number of children under the age of 15 with diabetes in the country today vary widely, ranging from 15,000 to 50,000. The facilities available in the 15 camps listed earlier in this paper would provide for less than 1,000 of these. It is obvious that more camps should be established, particularly in those regions of the country not now served. The establishment and maintenance of a camp is a costly process but entirely feasible, since it will in part pay for itself by fees from the campers and because a nonprofit project of this type for children finds a ready response from many donors.

The problem arises of what should be the primary aim of a summer camp for diabetic children. Answers to inquiries sent to those operating camps at the present time show considerable variation in purpose. Some have regarded the summer camps chiefly as a means for providing recreation and others chiefly as a method of providing good diabetic care and instruction for at least a small portion of each year. Our experience leads us to conclude that both aspects are important and that real success consists in a proper balance between the two. The diabetic child deserves an enjoyable vacation and at the same time the benefit of careful supervision. In keeping with this thought, we plan a variation in program in which during the third week of each three-week session the camper will be relieved of many of the routine laboratory studies. During this week an attempt will be made to approximate home conditions and the camper allowed to assume guided responsibility for urine testing, administration of insulin, and other duties.

So far in this discussion nothing has been said regarding the rest afforded the parents of a child during the few weeks at a summer camp. During this time the parent is allowed relief from tension, worry, and fatigue which may develop from the constant responsibility imposed by the presence of the diabetic child in the household. Moreover, the instruction received by the child should make the task of the parent easier during the rest of the year.

SUMMARY

Data obtained at a summer camp for diabetic boys are presented. The background, value, and place of such a camp are outlined.

During the 1950 season 138 boys were cared for at the Elliott P. Joslin Camp for three to nine weeks. The fact that the campers came from areas so widely distributed emphasizes the need for other diabetic camps throughout the country.

The following is a summary of data regarding 135 of the campers: Ages ranged from 5 to 16.9 yr., heredity was positive in 62%, duration of diabetes varied from 0.4 to 13.1 yr., and heights and weights were somewhat greater than those of non-diabetic boys of comparable ages. Diets prescribed at discharge varied from an average of 183 gm. carbohydrate, 85 gm. protein, 91 gm. fat, and 1,891 Cal. in the age group 5 to 7.9 yr. to 223 gm. carbohydrate, 130 gm. protein, 129 gm. fat, and 2,573 Cal. in the age group 14 to 16.9 yr. Various insulin programs were used, but 99 of the 135 boys were discharged either on a single dose of NPH insulin or a mixture of crystalline and NPH insulin daily. The degree of control obtained by NPH insulin alone or with a small addition of crystalline insulin was essentially the same as that obtained by separate injections of crystalline and protamine zinc insulin. Hypoglycemic reactions occurred with about equal frequency on the various insulin programs used. Little or no evidence of degenerative vascular complications was evident in this group of campers of which nine had had diabetes for 10 yr. or more.

Behavior problems are discussed and their importance indicated.

Methods of operating a summer camp for diabetic children are discussed, and the need for the establishment of other camps is stressed.

RELATIONSHIP OF EEG FINDINGS TO CLINICAL FACTORS DURING AND AFTER ACUTE PURULENT MENINGITIS

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IT IS WELL known that acute purulent meningitis in infancy and childhood may be followed by mental defect, neurologic abnormalities, changes in behavior, or recurrent convulsive seizures. Recent methods of treatment have resulted in dramatic reduction in mortality rates for all types of acute purulent meningitis. As more and more children survive the initial onslaught, the problem of residual disability becomes increasingly important. In every case, the question arises, Will this child's subsequent development be normal?

On clinical grounds alone one can usually predict with some degree of accuracy which children will probably return to normal. It would be of practical value, however, if more sensitive methods were available for determining the extent of damage and relating this to the likelihood of subsequent disability. For this reason, we have used electroencephalography during and after acute purulent meningitis in order to determine whether it is useful as a prognostic tool in this disease. Furthermore, we think such findings may be of interest because there have been no other reports of follow-up electroencephalographic studies in a large group of patients with acute purulent meningitis.

It is the purpose of this paper to report the electroencephalographic findings in 40 children with acute purulent meningitis, 29 of whom were under 2 yr. of age at the time of the initial tracing, and to correlate serial electroencephalograms with the presence or absence of disability. Tables 1 and 2 indicate, respectively, the age distribution of the patients and the type of meningitis.

METHODS OF TREATMENT OF MENINGITIS

Diagnosis of the type of meningitis was determined by Gram stain, by cultures of the spinal fluid and blood, and by specific typing of organisms found in the spinal fluid. Identification of the etiologic agent was sometimes prevented by previously administered sulfonamides or penicillin given before hospitalization. Treatment was instituted promptly and included the simultaneous use of two or more antibacterial agents, since in some instances the causative organisms could not be identified with accuracy except by culture methods, or not at all. In most cases, however, the etiologic agent was ascertained prior to culture. In view of danger

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to life and to the brain, we favored an antibacterial barrage—so-called broad coverage—especially since there was not always an opportunity to type the susceptibility of the various organisms and to determine the blood levels of the antibacterial agents.

Upon diagnosis of any type of acute meningitis, the patient was immediately given a subcutaneous injection of 1 grain per pound (0.15 gm. per kilogram) of sulfadiazine sodium. Sulfadiazine was continued in a dose of 2 grains per pound (0.3 gm. per kilogram) per day. For the first two days it was given subcutaneously in four equal injections at six-hour intervals. When it could be well-tolerated by mouth, the same dose was given orally, but in six equal doses at four-hour intervals. Use of sulfadiazine was usually continued for about two weeks after the temperature became normal but was discontinued earlier for patients who had meningococcic meningitis. Toxic reactions to sulfonamides were practically negligible. Determination of blood levels of sulfonamides was followed carefully, and attempts were made to maintain the level between 10 and 15 mg. per 100 cc. of blood. When the temperature became normal, the dose of sulfadiazine was reduced to 1 grain per pound (0.15 gm. per kilogram) per day.

TABLE 1.—*Age Distribution of Forty Patients with Acute Purulent Meningitis*

Age Group	Number of Patients
0-12 mo.	19
13-24 mo.	10
25-36 mo.	4
37-48 mo.	4
49-60 mo.	0
5- 6 yr.	1
7- 8 yr.	2

TABLE 2.—*Distribution of Forty Patients According to Type of Meningitis*

Type	Number of Patients
Influenzal	19
Pneumococcic	8
Meningococcic	1
Undetermined *	12

* We believe from our data that the undetermined cases were actually influenzal, 6; pneumococcic, 1, and unknown, 5.

Each patient was given 30 cc. per kilogram per day of ⅙ M solution of sodium lactate by subcutaneous injection with the sulfadiazine sodium in order to alkalinize the urine and to help counteract the acidosis present in this acute febrile illness. After oral medication was possible, 5 cc. per kilogram per day of molar sodium lactate was given by mouth in fruit juice in three or four doses. Other fluids were given to assure a good output of urine, especially in the initial stages of treatment with sulfadiazine, since there is real hazard to the kidneys if a dehydrated child is given large doses of a sulfonamide without the simultaneous administration of sufficient fluids to correct anhydremia.

The second drug used in each case was penicillin. Extremely high doses were probably far in excess of what is required. These large doses were given in order to overwhelm the organisms as quickly as possible, especially those with relative resistance to penicillin. We were unable to determine susceptibility to antibiotics on all patients and, therefore, felt justified in using large doses. Furthermore, we have favored intrathecal therapy less with the passing years. Only four out of the eight patients with pneumococcic meningitis received penicillin by intrathecal injection. The initial dose of crystalline penicillin was 1,000,000 units given intramuscularly. Thereafter, 200,000 to 500,000 units of crystalline penicillin was injected every three hours for at least a week, and sometimes longer. Penicillin therapy was discontinued sooner in cases of meningitis due to the Meningococcus, but was continued for about two weeks in cases of pneumococcic or influenzal meningitis.

The third antibacterial agent employed was dihydrostreptomycin. In this series of cases this drug was used only for patients with influenzal meningitis and those whose etiologic organism was not determined by stained smears of the centrifuged spinal fluid sediment, use of typing serum, or cultures. When the organism could not be determined by smears of the spinal fluid and the use of typing serum, dihydrostreptomycin was given immediately, and its subsequent use was evaluated according to the organism revealed by cultures. The initial dose of dihydrostreptomycin was 50 mg. per kilogram body weight given intramuscularly. Thereafter, 50 mg. per kilogram per day was given intramuscularly in four equal injections at 6-hr. intervals. Use of dihydrostreptomycin was discontinued after the fifth day in all cases except one, since influenzal organisms often build up resistance to the drug rapidly, and because there is danger of toxic damage from long-continued use.

No neurologic damage from dihydrostreptomycin was noted when the drug was given for five days, but one infant to whom it was administered for 11 days by intramuscular injection was subsequently deaf. Whether this was due to the disease or the drug is not known. Intrathecal injections of streptomycin were used in only three of the 19 cases of influenzal meningitis.

Recently, patients with influenzal meningitis have been given chloramphenicol (chloromycetin®). An immediate dose of 100 mg. per kilogram was given orally, and, thereafter, 50 to 100 mg. per kilogram per day was given in four to six equal doses.

TABLE 3.—*Duration of Follow-Up Studies*

Group	Duration, Mo.	Number of Patients
A	Less than 1	13
B	1	2
C	1-3	2
D	3-6	2
E	More than 6	20
F	Died	1
	Total	40

METHOD OF STUDY

1. *Technique.*—Standard techniques for assuring valid tracings were employed. The machine used was an Offner (Type C144) four-channel crystograph electroencephalograph. Ten electrodes, and sometimes more, were applied in the following positions: Two frontal, two parietal, two temporal, two occipital, and two as earring references. Various combinations of scalp-to-ear and scalp-to-scalp leads were employed. In some cases, sedation with secobarbital (seconal®) sodium was used, and allowance was made for this in interpretation of the tracings obtained.

2. *Rating of the Electroencephalogram.*—The electroencephalograms were rated normal, borderline normal, borderline abnormal, and abnormal. A modification of the Davis rating scale [1] was made, with special attention given to Gibbs's studies on normal children [2] and to the developmental tables of Lindsley, Smith, and Bernhard and Skoglund.[3] The studies made by Gibbs and Gibbs were also used as the criteria for determining normality in sleep.[4]

1. Davis, P. A.: Technique and Evaluation of the Electroencephalogram, J. Neurophysiol. **4**:92, 1941.

2. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, ed. 2, Cambridge, Mass., Addison-Wesley Press, Inc., 1950, Vol. 1: Methodology and Controls.

3. Lindsley, D. B.: Electrical Potentials in the Brain of Children and Adults, J. Gen. Psychol. **19**:285, 1938; Longitudinal Study of Occipital Alpha Rhythm in Normal Children: Frequency and Amplitude Standards, J. Genet. Psychol. **55**:197, 1939. Smith, J. R.: The Electroencephalogram During Normal Infancy and Childhood: II. The Nature and Growth of the Alpha Waves, ibid. **53**:455, 1938. Bernhard, C. G., and Skoglund, C. R.: On Alpha Frequency of Human Brain Potentials as Function of Age, Scandinav. Arch. Physiol. **82**:178, 1939.

4. Gibbs, E. L., and Gibbs, F. A.: Electroencephalographic Changes with Age During Sleep, presented at the 4th annual meeting of the American Electroencephalographic Society, June, 1950. Gibbs and Gibbs.[2]

3. *Follow-Up.*—Electroencephalograms were obtained during hospitalization, one month later, and every three months thereafter. In spite of efforts to bring all of the patients back for serial studies, we have been unable to follow the entire group as long as desired. Also, some of the children have had meningitis quite recently. Table 3 indicates the duration of follow-up studies.

In addition to the electroencephalogram, at each return visit a careful interim history and a complete physical examination were obtained with special reference to neurologic evaluation.

RESULTS

The results of this study will be discussed from the following standpoints: (1) changes in electroencephalographic patterns during and after acute purulent meningitis, and (2) correlation of serial electroencephalograms with clinical factors, namely, how soon treatment was instituted after the onset of the disease, speed of response, and subsequent development of neurologic disability, recurrent convulsive seizures, mental defect, and changes in the emotional pattern.

Changes in Electroencephalograms During and After Meningitis.—It must be stated at the start of this discussion that none of the children had had electroencephalograms made prior to the onset of meningitis. Since it is well-known that clinically normal individuals may at times have abnormal electroencephalograms, it is possible that an occasional child in this series may have had cerebral dysrhythmia before contracting meningitis. However, in view of the high percentage of patients who had abnormal initial electroencephalograms, it is hardly likely that this factor could have influenced the study appreciably. Figures 1 to 7 illustrate electroencephalograms taken during and after acute purulent meningitis.

In general the electroencephalographic changes can be considered in three chronological categories: (1) findings during the acute phase of meningitis, which we have arbitrarily called the first two weeks of the disease; (2) findings during the convalescent stage, which for present purposes is considered to be from two to six weeks after onset of meningitis, and (3) changes which persist longer than six weeks.

Acute Phase: The electroencephalographic changes in the acute stage of meningitis have been described by others,[5] and our findings are in agreement with theirs. In general, these electroencephalograms were characterized by marked irregularities in amplitude and rhythm appearing in all leads. The wave form most often observed in this stage of the disease was one of slow frequency and high microvoltage, appearing asynchronously from various regions of the cortex. In both the waking and sleeping states, there were occasional bursts of exceptionally high-microvoltage slow activity occurring in all areas simultaneously. Allowance was made in the interpretation of the tracings for the high, slow paroxysmal waves normally seen in the drowsy state in children, and these hypersynchronous episodes were not confused with the waves just mentioned. The normal changes occurring during drowsiness and sleep had to be kept in mind constantly, since the age group of the patients studied was that in which sleep changes might easily be confused with abnormal brain potentials.

5. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Addison-Wesley Press, Inc., 1945, pp. 110 and 157. Cohn, R.: Clinical Electroencephalography, New York, McGraw-Hill Book Company, 1949, pp. 268, 270 and 284.

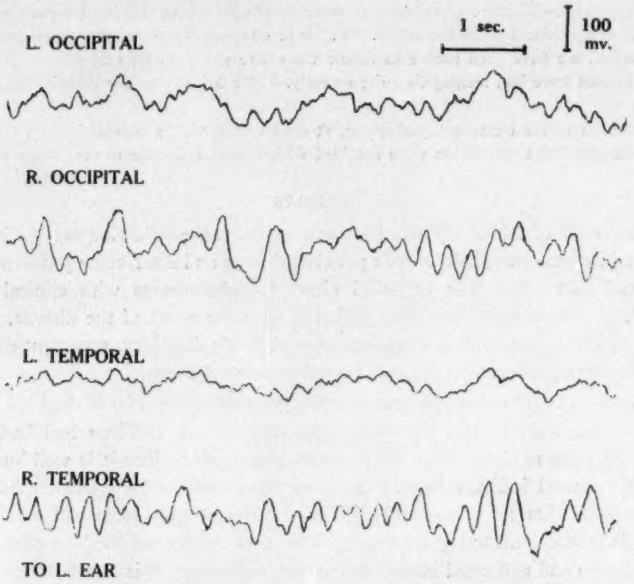

Fig. 1.—S. W., 18-mo.-old boy. Initial electroencephalogram taken in awake state 15 days after onset of influenzal meningitis. Note asymmetry of brain potentials from both hemispheres in scalp-to-ear tracings, and slow waves of high amplitude in the right occipital and right temporal leads. The patient was clinically normal at the time the tracing was made.

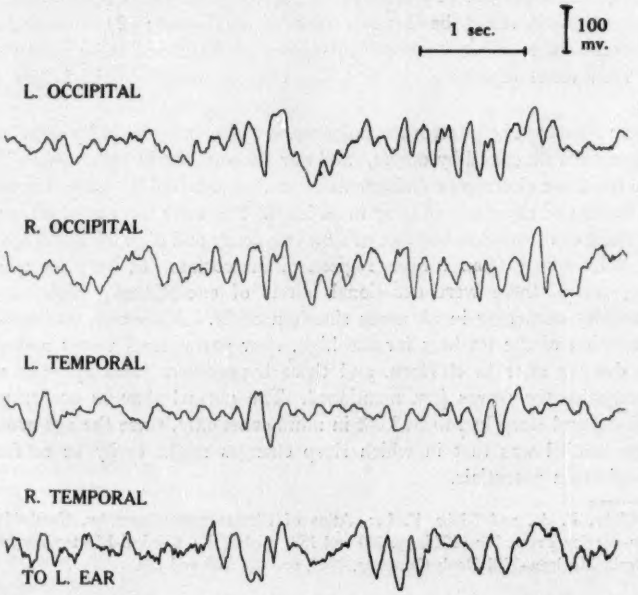

Fig. 2.—Electroencephalogram on same child six months after meningitis, when he was clinically normal. The tracing was taken in a drowsy state. The asymmetry previously noted has practically disappeared and the tracings are within normal limits.

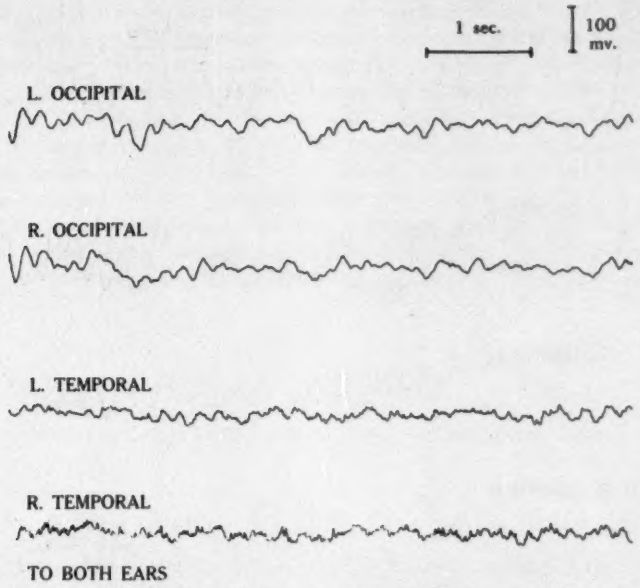

Fig. 3.—Electroencephalogram on same child 12 months after meningitis, when he was clinically normal. The electroencephalogram was taken in an early drowsy state. The tracing is within normal limits. The low-amplitude fast activity in temporal regions is a tension artifact.

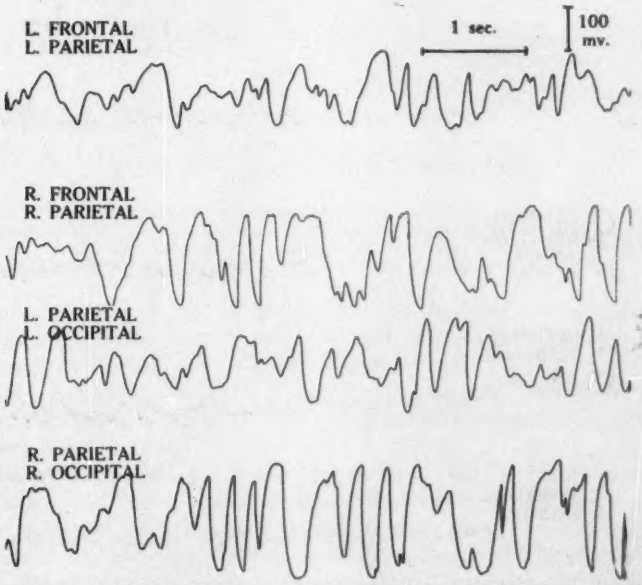

Fig. 4.—C. N., 14-mo.-old boy. Electroencephalogram obtained in the awake state two and one-half months after influenzal meningitis. There were persistent mental defect, behavior abnormality, and neurologic changes. The tracing shows asymmetry, slow waves of high microvoltage, and spike and wave activity with a grand-mal component.

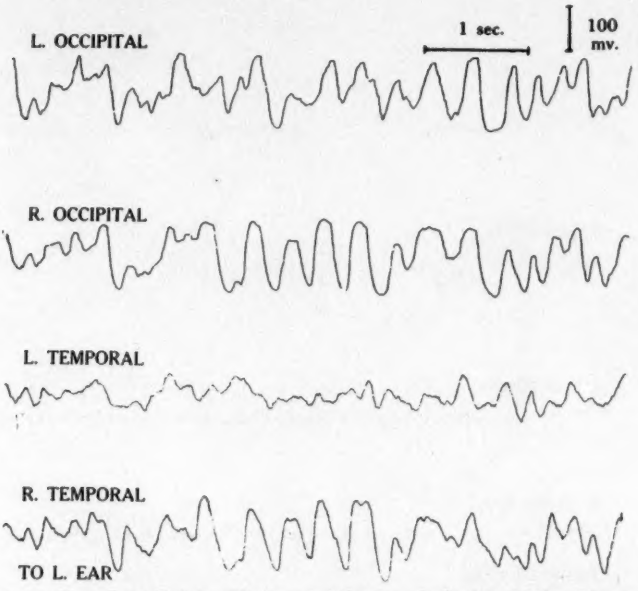

Fig. 5.—G. K., a 5-yr.old boy. Electroencephalogram obtained in awake state two weeks after onset of pneumococcic meningitis. The boy was clinically normal. The electroencephalogram shows irregularity and slow waves of high microvoltage.

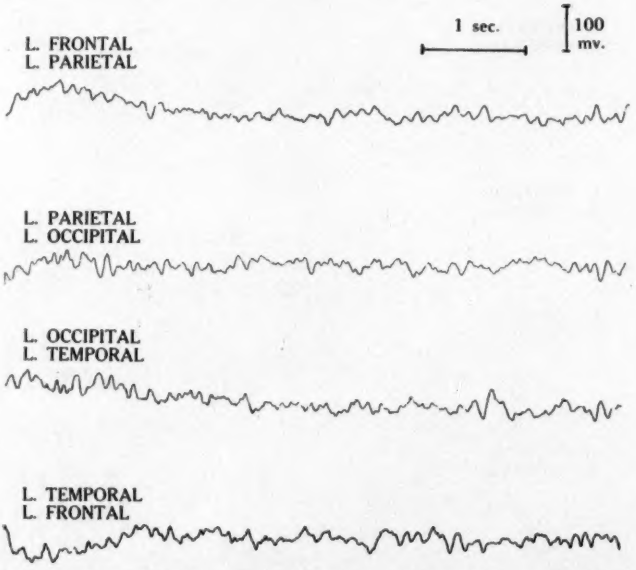

Fig. 6.—C. B., a 7-yr.-old boy. Electroencephalogram obtained in awake state four and one-half months after onset of an undetermined type of meningitis. The boy was clinically abnormal, with a neurologic defect, but the electroencephalogram was normal.

In addition to the slow activity and high microvoltage, which was the dominant factor in all the abnormal electroencephalograms in the acute stage, a few tracings also showed suppression of amplitude associated with a high percentage of fast activity. In these cases, such changes were usually generalized. However, in two patients, this low-amplitude fast activity was localized. In one of these infants a cystic hygroma developed in the right subdural area and an inflammatory dural membrane on the left. In the other infant bilateral enlargement of the lateral ventricles and cortical atrophy developed. Since only one subdural hygroma was detected in this series of patients, we have insufficient data on which to base any statement regarding the usefulness of electroencephalography in the diagnosis of this lesion. It is interesting to note that the patient who had a right subdural

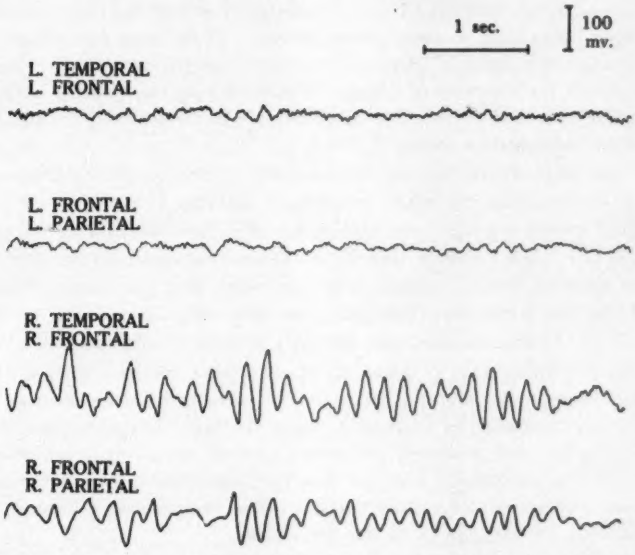

Fig. 7.—G. L., a 21-mo.-old girl. Electroencephalogram obtained in awake state 35 days after onset of pneumococcic meningitis. Subdural membrane on right and inflammatory dural membrane on left. Electroencephalogram shows suppression over area of membrane and slow sharp waves over the subdural hygroma.

hygroma had only strabismus on the left but had spasticity and increased deep reflexes in the right leg and weakness in the right arm associated with the inflammatory dural membrane over the left hemisphere. Tracings from this entire area showed low-amplitude fast activity, whereas those from the right hemisphere showed amplitude and frequency within normal limits except for slowing and frequent slow spikes over the occipital and temporal area.

"Convalescent" Stage: During the "convalescent" stage, which we are calling the period between two weeks and six weeks after the onset of meningitis, a gradual reduction in the amount of slow activity was noted in the electroencephalograms. There were no cases in which there was a sudden dramatic regression of abnormal activity. The shortest time interval between an initial electroencephalogram rated

as abnormal and a subsequently normal tracing was six weeks. However, in this case, the first electroencephalogram was obtained three weeks after the onset of meningitis; hence it was two months and one week from onset of illness to the date of the normal tracing.

The practical question arises, Does a normal electroencephalogram in a child who is recovering or has just recovered from acute purulent meningitis mean that the tracing will continue to be normal? Furthermore, how soon after the onset of meningitis can an electroencephalogram be obtained which will be of prognostic value? Our data show that 18 patients had normal initial electroencephalograms, and that these initial tracings were taken between six and 51 days after the onset of the disease. Eleven of these 18 patients have had serial tracings, and of these 11 there were seven who continued to have completely normal tracings without any shift toward an abnormal pattern of activity. Cortical function is considered to have been unimpaired in these seven patients. There were two whose subsequent electroencephalograms showed tendencies toward abnormality but still remained within the spectrum of normal. The remaining two patients shifted into the borderline abnormal range. One later returned to a completely normal pattern and the other to borderline normal.

Since our study shows that one may encounter a normal electroencephalogram as early as six days after the onset of meningitis and that 15 out of the 18 patients with initially normal tracings were studied less than three weeks after the onset of the disease, one might conclude that the initial electroencephalogram obtained for prognostic purposes should be taken about one month after the onset of illness. In the event that this initial electroencephalogram shows any abnormality, serial tracings should be obtained subsequently, probably at three-month intervals.

Changes Persisting Longer Than Six Weeks After Onset.—In those children whose electroencephalograms did not return to normal, the changes noted in the initial tracings persisted. In addition to these findings, the appearance of sharp waves with spikes was observed, sometimes isolated, occasionally in spike-dome conformation. In one patient who had recurrent convulsions, the grand-mal component was also present. In those cases in which suppression persisted, it was usually localized to one area or to one hemisphere.

In 19 children who had follow-up electroencephalograms ranging from six to 17 mo. after the onset of meningitis, the final tracing was normal in 12 cases, borderline normal in 2, borderline abnormal in 2, and definitely abnormal in none.

Correlation of Initial Electroencephalogram with Clinical Factors.—It is an established fact that the earlier effective treatment is instituted in acute meningitis the less the damage to the brain. Therefore, we have been interested in correlating the nature of the initial electroencephalogram with the time from onset of meningitis to the start of treatment, speed of response, and clinical status at the time of the first electroencephalogram. Table 4 gives these data.

Treatment Instituted on First Day of Illness: It will be noted that in 16 children whose treatment began within 24 hr. after the onset of meningitis, the initial electroencephalogram was normal in seven instances, borderline normal in one, borderline abnormal in three, and definitely abnormal in five. The time between onset of the disease and the initial electroencephalogram varied from six to 51 days, with 10 out of the 16 patients having their first tracing less than 20 days

after the disease started. Three of these 16 patients were clinically abnormal when studied, on the 19th, 29th, and 35th days, respectively. Of these three patients, one was blind and apparently deaf, one had neurologic and mental abnormalities and changes in behavior when observed for a period of nine months following meningitis, and the third patient has been seen so recently that adequate follow-up is not yet possible. No patient treated on the first day of the disease who became clinically

TABLE 4.—*Relationship of Initial Electroencephalograms to Time Treatment Was Started, Speed of Response, and Clinical Status*

Onset to Treatment, Days	Speed of Response *	Clinical Status	EEG Rating †	Onset to 1st EEG, Days
1	R	Normal	N	9
1	R	Normal	N	10
1	R	Normal	N	35
1	R	Normal	BA	18
1	R	Normal	BA	20
1	R	Normal	A	37
2	R	Normal	N	8
2	R	Normal	N	9
2	R	Normal	N	11
2	R	Normal	N	13
2	R	Normal	BA	23
2	R	Abnormal	BA	25
3	R	Normal	N	10
3	R	Normal	N	13
3	R	Normal	N	13
3	R	Normal	A	14
1	M	Normal	N	6
1	M	Normal	BN	10
1	M	Normal	N	14
1	M	Normal	A	15
1	M	Normal	BA	14
2	M	Abnormal	A	4
2	M	Normal	BA	17
3	M	Normal	N	12
3	M	Normal	N	16
3	M	Normal	BN	17
3	M	Abnormal	N	39
4	M	Abnormal	BN	18
1	S	Normal	N	18
1	S	Normal	N	51
1	S	Abnormal	A	19
1	S	Abnormal	A	29
1	S	Abnormal	A	35
2	S	Normal	N	21
2	S	Abnormal	A	24
3	S	Abnormal	BA	13
3	S	Abnormal	A	32
3	?	Abnormal	A	2
3	?	Abnormal	A	2 yr.
1	Death	.....	..	..

* Code for speed of response: R, rapid (afebrile and normal in 3 days); M, moderate (afebrile and normal in 1 week); S, slow (fever longer than 1 week and clinically abnormal).
† Code for EEG ratings: N, normal; BN, borderline normal; BA, borderline abnormal; A, abnormal.

normal before discharge showed any subsequent disability. While this might indicate that clinical evaluation alone suffices for accurate prognosis, it is to be noted that two patients whose subsequent clinical course was normal still had borderline tracings at the time of the last follow-up studies 12 and 13 mo., respectively, after onset of meningitis. A third child, whose first electroencephalogram was borderline abnormal at the time an initial clinical evaluation was normal, has not yet returned for follow-up studies.

Treatment Instituted on Second Day of Illness: Of 10 children whose treatment began two days after onset of meningitis, the initial electroencephalogram was normal in five instances, borderline abnormal in three, and abnormal in two. The time between onset of the disease and the initial tracing ranged from four to 25 days, with six of the 10 patients having their first tracing less than 20 days after onset of meningitis. Three of these 10 patients were clinically abnormal when studied, respectively, on the 4th, 24th, and 25th day of the disease. The child who was abnormal on the fourth day of illness rapidly improved, to become persistently normal; thus only two of the 10 children remained clinically abnormal when treatment was started on the second day of the disease. At the time of discharge, both of these children had neurologic and mental defect, and one had behavior changes. Follow-up study was impossible in both cases, since one patient moved out of the city and the mother of the other refused to have further studies on her child. No patient treated on the second day of illness who was clinically normal on discharge was clinically abnormal later. In this group there were no patients who remained clinically normal but had abnormal electroencephalograms.

Treatment Instituted on Third Day of Illness: Of 12 children whose treatment began three days after onset of meningitis, the initial electroencephalogram was normal in six instances, borderline normal in one, borderline abnormal in one, and abnormal in four. In 11 of the 12, the time between onset of the disease and the initial tracing ranged from three to 39 days. The 12th case was first studied electroencephalographically 2 years after meningitis, which was treated elsewhere. Five of the 12 patients were clinically abnormal when studied, respectively, the following times after onset of illness: 3 days, 13 days, 32 days, 39 days, and 2 years. The child first studied three days after the onset of meningitis did not return for follow-up studies, but when discharged had neurologic, mental and behavior abnormalities, and repeated convulsions. Residual defects of the other 4 children were as follows: One had brain atrophy, as shown by pneumoencephalography, and was retarded mentally; one had neurologic defects alone; one had neurologic and mental defect and behavior abnormalities, and one had recurrent convulsions and neurologic and mental defect. No patient first treated on the third day of illness who was clinically normal on discharge was clinically abnormal later, but two of these seven clinically normal patients continued to have borderline electroencephalograms.

Other Cases: In the single case in which the first treatment was given four days after the onset of meningitis, the initial electroencephalogram, taken 18 days after the onset of illness, was borderline abnormal. After a 15-mo. follow-up period, the electroencephalogram for the first time came within normal limits. Clinically, the child is deaf but otherwise normal. Since dihydrostreptomycin was given to this child in a dose of 50 mg. per kilogram of body weight per day for 11 days, there is a question whether the deafness may have been caused by the drug. There was no intrathecal medication in this case.

No comment will be made concerning the child who died, except to say that he was treated one day after the onset of pneumococcic meningitis.

Relationship of Initial Electroencephalogram to Speed of Clinical Response.— In regard to speed of clinical response, we divided our cases arbitrarily into three categories: (1) rapid response, in which the child was afebrile within three days

after the institution of treatment and was clinically normal; (2) moderately rapid response, in which fever disappeared within a week and the child seemed normal, and (3) slow response, in which fever persisted longer than a week and in which there were other clinical signs that the child was doing poorly. Unfortunately, subdural taps were not performed in the latter group to rule out subdural effusions, which have recently been held partially accountable for the persistence of abnormal clinical findings in purulent meningitis.[6]

By these criteria, the 37 cases in which speed of response was observed were divided as follows: rapid response, 16 cases; moderately rapid, 12 cases; and slow, 9 cases. Two patients were treated elsewhere, and there was inadequate clinical information to ascertain speed of response. One patient out of the 40 died after one month of treatment and is not considered in the follow-up. Autopsy on this patient revealed pneumococcic meningitis, bronchopneumonia, and interventricular septal defect.

Table 5 shows the correlation between initial tracings and speed of clinical response. It will be noted that of the 16 cases with a rapid response the initial electroencephalogram was normal in 10 instances, borderline abnormal in 4, and

TABLE 5.—*Correlation of Initial Electroencephalogram with Speed of Response*

Speed of Response	Number of Cases *	Rating of Initial EEG			
		Normal	Borderline Normal	Borderline Abnormal	Abnormal
Rapid	16	10	0	4	2
Moderate	12	5	2	3	2
Slow	9	3	0	1	5

* Three cases are not included: One patient died and two were treated initially elsewhere.

abnormal in 2. Of the 12 cases with moderately rapid response, the initial tracing was normal in 5 cases, borderline normal in 2, borderline abnormal in 3, and abnormal in 2. Of the nine cases with slow response, the initial electroencephalogram was normal in three instances, borderline abnormal in one, and abnormal in five. These findings indicate, as would be expected, that children with meningitis who respond rapidly to treatment are more likely to have normal initial electroencephalograms, and that those whose clinical response is slower tend more to have abnormal brain potentials. How soon can a normal electroencephalogram be expected in children with a rapid response to therapy? Of the 16 children with rapid clinical response, the tracing obtained in the second week of the disease was normal in nine cases and might have been normal earlier in a 10th child whose initial electroencephalogram was recorded on the 35th day of the disease.

Correlation of Serial Electroencephalograms with Clinical Examinations.—To what extent in acute purulent meningitis is electroencephalography more sensitive in determining the status of the nervous system than clinical examination alone? Table 6 shows the correlation between rating of electroencephalograms and clinical

6. Smith, M. H. D.; Dormont, R. E., and Prather, G. W.: Subdural Effusions Complicating Bacterial Meningitis, Pediatrics **7**:34, 1951. McKay, R. J., Jr.; Morisette, R. A.; Ingraham, F. D., and Matson, D. D.: Collections of Subdural Fluid Complicating Meningitis Due to Hemophilus Influenzae (Type b), New England J. Med. **242**:20. 1950.

evaluation in all of the studies made. The purpose of this table is to determine to what extent electroencephalography is more sensitive than clinical evaluation in detecting cortical abnormality, and, on the other hand, to find out how often the tracing is normal when the child is clinically abnormal. It will be noted that in 74 instances in the serial studies when the clinical evaluation was normal the electroencephalogram was clearly normal in 63% of the cases, borderline normal in 11%, borderline abnormal in 18%, and definitely abnormal in 8%. On the other hand, in 25 instances when the clinical examination was clearly abnormal, the electroencephalogram was normal in 20% of cases, borderline normal in 8%, borderline abnormal in 20%, and definitely abnormal in 52%.

If we consider ratings of normal and borderline normal as being within normal limits and abnormal and borderline abnormal as being within the abnormal range, the following facts emerge: 1. In 74 instances, when the clinical examination was normal the electroencephalogram was within normal limits in 74% of cases and abnormal in 26%. 2. In 25 instances, when the clinical status was abnormal the electroencephalogram was within normal limits in only 28% of cases and

TABLE 6.—*Correlation of Electroencephalogram with Simultaneous Clinical Examination in Ninety-Nine Studies on Forty Patients*

	Rating of EEG			
Clinical Examination	Normal	Borderline Normal	Borderline Abnormal	Abnormal
Normal (74 examinations)	47	8	13	6
Abnormal (25 examinations)	5	2	5	13

abnormal in 72%. Thus, approximately one out of four children who appeared to be normal had an abnormal tracing, whereas about one out of four who were clinically abnormal had a normal tracing. Therefore it becomes apparent that neither clinical examination nor electroencephalography alone suffices for adequate evaluation, but that the two should be weighed together to determine the status of the patient. From our studies on acute purulent meningitis we believe that electroencephalography has the following practical applications: (1) to detect damage to the brain in children who are clinically normal, and (2), through improvements in serial electroencephalograms, to yield information of prognostic value.

SUMMARY AND CONCLUSIONS

1. Electroencephalograms were obtained on 40 patients during the acute stage of purulent meningitis and at intervals thereafter, and in each instance clinical evaluation was performed at the time of the electroencephalogram.

2. The data were analyzed from the standpoint of age of patient, type of meningitis, time from onset to start of therapy, speed of clinical response, changing patterns in the serial electroencephalograms, and presence or absence of residual disability.

3. Four factors especially considered in follow-up examinations were mental defect, neurologic abnormalities, changes in behavior, and recurrent convulsive seizures.

4. The most constant abnormalities in the electroencephalograms during the first two weeks after onset were (1) marked irregularities in amplitude and rhythm in all leads, (2) a dominant pattern of slow waves of high amplitude, and (3) in some instances low-amplitude fast activity.

5. From two to six weeks after onset of the disease, the chief change noted was a gradual reduction in the amount of slow activity.

6. After six weeks there was a marked tendency for the electroencephalogram to return to normal. In those children who showed a slower return to a normal pattern of activity, the patterns of the initial tracings persisted, sometimes for several months, with the occasional appearance of sharp waves.

7. From the electroencephalographic standpoint, the eventual outcome in 19 patients followed for periods ranging from six to 17 mo. were as follows: 12 were normal; 3, borderline normal; 2, borderline abnormal, and none, definitely abnormal. However, five of our patients who had the most abnormal initial electroencephalograms failed to return for follow-up studies. Parents of some of these patients stated that the children were so badly damaged mentally and neurologically that they did not wish to have further studies made.

8. Of 26 children treated within two days of onset, only five were clinically abnormal when last evaluated, whereas of 12 first treated on the third day, 5 were clinically abnormal when last studied.

9. Children who have become clinically normal after meningitis may continue to have electroencephalographic abnormalities for variable periods, but in most instances the electroencephalograms tend to return to normal.

10. In this study, the initial electroencephalogram was normal in 10 out of 16 cases of children with a rapid clinical response to treatment, normal in five out of 12 who responded with moderate rapidity, and normal in only three out of nine whose clinical improvement was slow.

11. In meningitis correlation between electroencephalograms and clinical examinations is not complete. However, approximately three out of four children who were clinically normal had electroencephalographic ratings within normal limits, whereas about three out of four children who were clinically abnormal had electroencephalographic ratings which fell within the abnormal range. In the cases of those who were clinically abnormal but had normal electroencephalograms, it is probable that damage produced in deeper-lying structures was not revealed in cortical brain potentials.

While the variability of clinical response in acute purulent meningitis is apparent, this study shows that the electroencephalogram may detect damage to the brain which is not obvious on clinical evaluation alone, and that serial electroencephalograms are of prognostic import.

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EXPERIMENTAL NUTRITIONAL MEGALOBLASTIC ANEMIA: RELATION OF ASCORBIC ACID AND PTEROYLGLUTAMIC ACID

I. Nutritional Data and Manifestations of Animals

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MINNEAPOLIS

A DEPENDABLE way has been found to produce a true megaloblastic anemia in monkeys, remarkably similar to that seen in humans, by means of deficient diets alone, without the use of drugs or vitamin antagonists. It became apparent from our experiments that ascorbic acid is involved in the metabolism of pteroylglutamic (folic) acid. A preliminary report has been made.[1] The following paper will provide more complete data concerning the diets, the symptomatology and blood of the animals, and the effect of various treatments.

Investigations have been made of the vitamin B_{12} and pteroylglutamic-acid content of the animals' diets, tissues, and excreta, and also of the metabolism of nucleic acids,[2] tyrosine,[3] and pigments. These items will be the topics of separate reports. It is expected that there will be another report extending the preliminary description of the findings in the blood and bone marrow.[4] Gross and microscopic pathological examinations were performed on all animals that died or were killed.[5]

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Acknowledgment is gratefully given to Lederle Laboratories, Division American Cyanamid Company, for materials which facilitated this study.

1. May, C. D.; Nelson, E. N., and Salmon, R. J.: Experimental Production of Megaloblastic Anemia; An Interrelationship Between Ascorbic Acid and Pteroylglutamic Acid, J. Lab. & Clin. Med. **34**:1724, 1949.

2. Lowe, C. U.; Barnum, C. P., and Terry, W. S.: Certain Quantitative Aspects of Nucleic Acid Metabolism in the Livers of Megaloblastic Monkeys, J. Lab. & Clin. Med. **36**:957, 1950.

3. Salmon, R. J., and May, C. D.: Metabolism of Tyrosine in Experimental Megaloblastic Anemia and in Scurvy in the Monkey, J. Lab. & Clin. Med. **36**:591, 1950.

4. May, C. D.; Nelson, E. N.; Salmon, R. J.; Lowe, C. U.; Lienke, R. I., and Sundberg, R. D.: Experimental Production of Megaloblastic Anemia in Relation to Megaloblastic Anemia in Infants, Bull. Univ. Minnesota Hosp. **21**:208, 1950.

5. Dr. James Dawson, professor of pathology, prepared the microscopic sections and made the histologic studies.

LITERATURE OF EXPERIMENTAL NUTRITIONAL MEGALOBLASTIC ANEMIA

It has long been felt desirable to have a dependable natural means of developing megaloblastic anemia in a suitable experimental animal to facilitate studies of metabolism and blood morphology and to test the effects of various compounds. Lucy Wills developed megaloblastic anemia by dietary means alone in monkeys as early as 1932 and used them to identify a factor effective in "nutritional" megaloblastic anemia and the megaloblastic anemia of pregnancy. This factor was demonstrated to be different from the anti-pernicious-anemia-principle in refined liver extracts.[6] Jukes and Stokstad have alluded to this as the first recognition of the factor now known as pteroylglutamic acid.[7]

Miller and Rhoads fed dogs a Goldberger "black-tongue-producing" diet. Macrocytic anemia developed, and the marrow was stated to be hyperplastic and "quite similar to that seen in sprue anemia or pernicious anemia."[8]

In 1935 Day and co-workers reported that leukopenia and anemia develop in monkeys fed diets lacking a factor which was designated as vitamin M,[9] which later was demonstrated to be pteroylglutamic acid.[10] Studies of the bone marrow of those monkeys have not yet been published.

The approaches to production of megaloblastic anemia in animals by utilizing drugs for suppressing the bacterial flora in the intestine to eliminate this exogenous source of vitamins or by using antagonists to pteroylglutamic acid, such as 4-amino-pteroylglutamic acid and methyl folic acid, are in a different category from our experiments.[11] It would not be pertinent to review these experiments.

CLINICAL INVESTIGATION OF MEGALOBLASTIC ANEMIA OF INFANCY AS A BACKGROUND

Clinical observation of infants in whom megaloblastic anemia had developed aroused our interest in the pathogenesis of this type of anemia in infancy. Since a single course of treatment with pteroylglutamic acid produced a lasting cure in these infants, it seemed that, among the possible causes, some feature of the diets might have permitted a deficiency of this substance to occur. This anemia usually

6. Wills, L.; Clutterbuck, P. W., and Evans, B. D. F.: A New Factor in the Production and Cure of Macrocytic Anemias and its Relation to Other Haemopoietic Principles Curative in Pernicious Anemia, Biochem. J. **31**:2136, 1937.

7. Jukes, T. H., and Stokstad, E. L. R.: Pteroylglutamic Acid and Related Compounds, Physiol. Rev. **28**:51, 1948.

8. Miller, D. K., and Rhoads, C. P.: Production in Dogs of a Syndrome Similar to Sprue by Diets Deficient in Vitamin B_6, Proc. Soc. Exper. Biol. & Med. **30**:540, 1933.

9. Day, P. L.; Langston, W. C., and Shukers, C. F.: Leukopenia and Anemia in the Monkey Resulting from Vitamin Deficiency, J. Nutrition **9**:637, 1935.

10. Day, P. L.; Mims, V.; Totter, J. R.; Stokstad, E. L. R.; Hutchings, B. L., and Sloan, N. H.: The Successful Treatment of Vitamin M Deficiency in the Monkey with Highly Purified Lactobacillus Casei Factor, J. Biol. Chem. **157**:423, 1945.

11. Heinle, R. W.; Welch, A. D., and Pritchard, J. A.: An Essentiality of Both the Anti-pernicious Anemia Factor of Liver and Pteroylglutamic Acid for Hematopoiesis in Swine, J. Lab. & Clin. Med. **33**:1647, 1948. Cartwright, G. E.; Palmer, J. G.; Tatting, Betty; Ashenbrucker, Helen, and Wintrobe, M. M.: Experimental Production of Nutritional Macrocytic Anemia in Swine: III. Further Studies on Pteroylglutamic Acid Deficiency, ibid. **36**:675, 1950. Thiersch, J. B., and Philips, F. S.: Effects of 4-Amino-Pteroylglutamic Acid in Dogs with Special Reference to Megaloblastosis, Proc. Soc. Exper. Biol. & Med. **71**:484, 1949.

occurred early in infancy, when the diets were composed principally of milk. It was further noted that these anemic infants were frequently deficient in ascorbic acid. On the basis of these clues, and referring to the work of Wills and Day, we undertook to produce megaloblastic anemia in young monkeys by feeding them milk diets deficient in ascorbic acid. The relation of the experimental megaloblastic anemia which resulted and the clinically occurring megaloblastic anemia in infancy has already been discussed in another paper.[12]

As may be seen in that account of our early experiments, a variety of milk diets were studied and no fundamental difference among them was noted. Therefore, for the purpose of this report, results with only a few readily available and easily reproducible diets will be given.

GENERAL ARRANGEMENTS OF EXPERIMENTS

We chose to work with monkeys because we felt that their nutritional requirements, as well as the morphology of the blood and bone marrow, were more like those of humans. It seemed that we might be more likely to duplicate the human disease which was the object of our study. At first we reared some monkeys on artificial milk feedings from the time they were born, thinking that the period of infancy might be crucial. We have learned that the age and sex of the monkey are relatively immaterial, although nearly all our animals were either newborn or immature (1.5 to 2.5 kg. in weight), or, as estimated from dentition, 10 to 15 mo. of age. Rhesus and cynomolgus monkeys behave identically. Immature animals have the advantage of enabling one to follow the weight curve as an index of their response to the experimental diets. The animals were housed in an uncrowded, light, well-ventilated, temperature-controlled (75 to 80 F.) room, in individual metabolism cages, which were thoroughly washed daily.

The monkeys, other than the newborn,[13] were acquired from regular animal dealers. They were kept under observation until they were seen to be in good health, tuberculin-negative, and eating well, and until preliminary studies were completed. During this preliminary period they were fed one of the milk diets provided for the control animals described in detail below. No pteroylglutamic acid or vitamin B_{12} was given. An intramuscular injection of 100 to 200 mg. of ascorbic aid was given to each animal soon after it was received, in order that all the animals would be equally saturated with this vitamin at the start of the experiments. This preliminary period sometimes extended over many weeks while necessary data were being gathered before the monkeys could be placed on one of the experimental regimens. The length of this period is given for each animal in Table 2. As will be seen, our experience suggests that if it is necessary to keep the animals for a preliminary period on a milk diet it would be desirable to keep it as short and as uniform as possible.

The monkeys were watched closely by the same observer, a physician. Daily record was made of any symptoms, particular attention being directed toward detection of diarrhea or respiratory infections. The animals were weighed weekly.

Blood counts and needle biopsy examinations of the marrow were done regularly at frequent intervals and whenever symptoms appeared, especially at the advent of anemia and when the animals were under treatment. Diets: The milk diets were offered in liquid form (150 to 200 cc. in the morning, and 300 to 400 cc. in the afternoon) in measured amounts. The volume of the morning feeding was restricted so that it would be completely consumed, but the afternoon feeding was adjusted to provide all the animal would eat. This arrangement assured ingestion of supplementary substances furnished in the milk and provision of adequate food for growth. The animals uniformly ate 400 to 600 cc. a day, or 200 to 300 cc. per kilogram of body weight.

12. May, C. D.; Nelson, E. N.; Lowe, C. U., and Salmon, R. J.: Pathogenesis of Megaloblastic Anemia in Infancy, Am. J. Dis. Child. **80**:191 (Aug.) 1950.

13. Dr. Syverton, professor of bacteriology, let us have newborn monkeys born in this local colony.

The intake could be noted with reasonable accuracy, as the animals generally learned to drink without spilling. Record of the intake is valuable because anorexia proved an early sign of impending megaloblastic anemia or sickness.

The diets utilized during the experiments are given in Table 1. The numbers given the diets correspond to those used in the previous report[12] of earlier experiments. It will be

TABLE 1.—*Basal Diets and Supplements*

Diet No.	Dates Used	Composition		Experimental Monkey	Control Monkeys
4	3 /1/49 to 12/20/49	Whole dried cow's milk *	13.5 gm.	5, 13B, 14B	4C, 7
		Lactose, U.S.P.	10.0 gm.	.....	.....
		Corn oil †	3.3 gm.	25	.....
		Water to make	200 cc.	.....	.....
4A	12/20/49 to 3 /7/50	Whole dried cow's milk *	13.5 gm.	5, 14B	7
		Corn syrup ‡	18 gm.	.....	.....
		Water to make	200 cc.	.....	.....
4B	Since 3/7/50	Whole dried cow's milk *	13 gm.	30, 32, 33, 37, 39, 40B, 45	4E, 67, 68
		Water to make	100 cc.	47, 48, 49, 50, 51	
5	6/ 2/48 to 3/ 3/50	Evaporated cow's milk	40 cc.	12A	4A
		Corn syrup ‡	4 gm.	.....	.....
		Water to make	100 cc.	.....	.....
7	11/28/49 to 5/25/50	Pasteurized fresh whole cow's milk, unaltered		24	23
8	Since 3/11/50	Soy bean flour synthetic infant food, § normal dilution		41	36A

Supplements to All Diets Listed in Table 1

B. Vitamins

Prior to 2/25/50:

3 cc. of following aqueous solution to vitamins daily in afternoon feeding:

Thiamine hydrochloride	0.05 mg. per cc.
Riboflavin	0.06 mg. per cc.
Nicotinic acid	0.04 mg. per cc.

Made up fresh every two weeks, stored in cold in amber-colored bottle

Since 2/25/50:

1 cc. intramuscularly weekly of solution ‖ containing:

Thiamine hydrochloride	5 mg.
Riboflavin	2 mg.
Nicotinamide	75 mg.
Sodium pentothenate	2.5 mg.
Pyridoxine hydrochloride	5 mg.

Vitamins A and D

Desynon® ¶ (water-miscible, 90% alcohol)

Vitamin A 500 I.U. per drop

Vitamin D 50 I.U. per drop

8 drops daily in the morning feeding

Iron

Elixir ferrous gluconate,** 4 cc. daily in afternoon feeding. This amount provides 25 mg. ferrous iron a day.

Ascorbic Acid

Control animals always received a 50 mg. ascorbic acid tablet daily, crushed and dissolved in the morning feeding. In addition after 3/25/50 all control animals were given 100 mg. ascorbic acid intramuscularly every two weeks.

* Klim, The Borden Company.

† Mazola, The Corn Products Company.

‡ Cartose, mixed detrin-maltose-dextrose, W. H. Kinney and Sons, Inc.

§ Mull Soy, The Borden Company.

‖ Betalin Complex, Eli Lilly & Company.

¶ Winthrop Chemical Company.

** Eli Lilly & Company.

Diets No. 4, 4A, 4B were treated to remove ascorbic acid after 11/25/49, by adding 1 drop of 5% $CuSO_4$ to each 100 cc., storing overnight in the refrigerator, and boiling for five minutes before feeding.

Diet No. 5 not heated prior to 7/26/49, boiled for five minutes before feeding thereafter; $CuSO_4$ treatment unnecessary.

Diet No. 7 boiled five minutes before feeding; $CuSO_4$ treatment unnecessary.

Diet No. 8 not boiled or treated with $CuSO_4$.

noted in Table 1 that the same supplementary substances were given along with each of the diets, except that only the controls received ascorbic acid during the experimental periods. The diets were analyzed for pteroylglutamic acid and vitamin B_{12} by microbioassay. While these data will be reported in detail later, it may be mentioned that the amounts were essentially the same in all the milk diets; namely 3 γ of pteroylglutamic acid per liter and 2 γ of vitamin B_{12} per liter. The soy bean flour formula (Diet No. 8) contained 30 γ of pteroylglutamic acid and 0.2 γ of vitamin B_{12} per liter. Precautions had to be taken to remove all ascorbic acid from the diets and later to restore ascorbic acid for the control animals. This is important, as even the traces of ascorbic acid which survive in the manufacture of evaporated milk and

dried whole milk were found to be sufficient to delay the onset of the megaloblastic anemia. The amount of ascorbic acid in the diets were checked by chemical analysis. Whereas boiling the diet five minutes sufficed to destroy all of the ascorbic acid in fresh whole milk and evaporated milk, it was necessary in the case of the whole dried milk to add $CuSO_4$, store 12 hr. in the cold, and then boil five minutes to destroy all the ascorbic acid. These manipulations did not affect the content of pteroylglutamic acid and vitamin B_{12}.

It was found that modification of the milk with different carbohydrates or fat and providing protein concentrations from 1.6 to 3.5 gm. per 100 cc. made no essential difference in our results. All the diets provided between 60 and 70 Cal. per 100 cc. For the past year we have simply used normal reconstituted whole dried cow's milk as our basal diet, treated with $CuSO_4$ and boiling, and then supplemented as indicated. For the sake of convenience, the dietary regimen we are now using to produce megaloblastic anemia in monkeys is provided (Appendix A).

MANIFESTATIONS OF THE EXPERIMENTAL ANIMALS

The sequence of events and the manifestations of the animals were so uniform that a composite account may be offered. Part of the data of some of the monkeys are depicted in graphic form to facilitate visualizing typical courses (Charts 1 to 6). The pertinent details from records of the individual animals will be presented in tabular form at the end of this report (Appendix B). In the following account reference to the animals by their numbers enables one to locate the original data in Appendix B on which any statement is based.

When the animals were fed the diets listed in Table 1 along with abundant ascorbic acid as indicated, they remained in good health, they usually gained weight, and megaloblastic anemia did not develop during the control periods (Fig. 1). These control periods were usually much longer than the period required for megaloblastic anemia to develop in all the animals receiving the corresponding diet without ascorbic acid. This can be seen more clearly in Table 2, which summarizes the duration of the experiments.

When the experimental animals were fed the diets and supplements as indicated in Table 1, without ascorbic acid, they gained weight and showed no signs of ill health, anemia, or change in the marrow for the first six to 12 weeks of the experimental regimen. As mentioned above, they were saturated with ascorbic acid before the start of the experiment. The first abnormality noted was usually diminution of appetite, revealed by reduced intake. This might be gradual but was often abrupt. They usually continued to eat about one-half their customary intake until the last few days of their illness when marked anorexia developed, the animals sometimes refusing to eat anything. A few animals retained a fair appetite, but the rest of the symptoms were not altered by this.

As the appetite failed, the weight gain ceased and a gradual decline began. Within one to two weeks a more precipitous deterioration occurred; then, after from 60 to 90 days without ascorbic acid, the first clinical signs of scurvy appeared (Chart 2). Swelling of the wrists and a disinclination to move or climb were probably the earliest dependable signs of scurvy. Periorbital hemorrhages always appeared, and, since this is such an overt symptom as to be indisputable, we chose to rely on this sign as evidence that scurvy was well established. Gingivitis is a deceptive sign, for with these liquid diets the gums are often boggy and inflamed and may bleed easily. However, when scurvy was evident, the gums became purpuric and necrotic, sometimes severely so with loosening of the teeth. A few

TABLE 2.—*Days to Onset of Scurvy and Onset of Megaloblastic Anemia, and Total Days on Diets*

Experimental diets with ascorbic acid, controls

Diet No.	Monkey No.	Total Days on Diet Without Megaloblastosis
4	4C	147
4 and 4A *	7	330
4B	4E	348
4B	67	198
4B	68	198
5	4A	264
7	23	177
8	36A	222

Experimental diets without ascorbic acid

Diet No.	Monkey No.	Days to Scurvy	Days to Megaloblastic Marrow †	Preliminary Period, Days ‡	Total Days on Diet §
4 and 4A *	5	307 ‖	311 (5)	0	311
4B	45	84	102 (18)	5	107
4B	47	70	90 (20)	2	92
4B	48	70	90 (20)	2	92
4B	49	83	98 (15)	1	99
4B	50	74	63 (—11)	2	74
4B	51	72	92 (20)	4	96
4B	33	119 ¶	129 (10)	59	188
5	12A	130 ‖	157 (27)	0	157
7	24	88	119 (31)	0	116
8	41	117	130 (13)	23	158

Experimental diets without ascorbic acid but supplemented with P. G. A., folinic acid or vitamin B_{12}

Diet No.	Supplement	Monkey No.	Scurvy	Marrow
4	15 γ B_{12} I. M. every 2 wk.	13B	90	Megaloblastic on 90th day
4 and 4A *	5 mg. P. G. A. by mouth weekly	14B	104	Normoblastic on 119th day
4B	500 γ P. G. A. I. M. weekly	30	76	Normoblastic on 98th day
4B	7.5 γ Vitamin B_{12} I. M. weekly	32	..	Megaloblastic on 50th day before any signs of scurvy
4B	500 γ P. G. A. 7.5 γ B_{12} I. M. weekly	37	71	Normoblastic on 94th day
4B	500 γ P. G. A. p. o. weekly	39	65	Normoblastic on 92nd day
4B	Folinic acid (see table in appendix for details)	40B	101	Normoblastic on 159th day

* Periods on these two diets are grouped together for the purpose of this table, as the protein contents are the same and no difference between them was noted.

† Numbers in parenthesis are days between onset of scurvy and appearance of megaloblastic marrow.

‡ Preliminary period:—Days on milk diet with ascorbic acid while preliminary data being collected before discontinuing ascorbic acid.

§ Total days before megaloblastosis, i. e., days on milk diet with ascorbic acid in preliminary period plus days on experimental diet without ascorbic acid.

‖ Traces of ascorbic acid found in diets (see text for further comment). After all ascorbic acid destroyed megaloblastic anemia appeared in 45 days for No. 5 and in 28 days for No. 12A.

¶ After 56 days without ascorbic acid received single dose of 100 mg. ascorbic acid by mistake and then no more.

roentgenograms of the wrists were made. Detectable signs of scurvy by this means appeared at about the time the animal began to lose weight, two to three weeks before clinical signs of scurvy were unmistakable. Abnormalities were never noted in the tongue.

With the appearance of scurvy, the weight loss and anorexia rapidly led to pronounced emaciation. The fur lost its color and luster, became ruffled, and occasionally was shed in large amounts. The animals sat quietly hunched in a corner of the cage and resisted handling only feebly. They moved about in a shuffling manner if at all but showed no evidence of paralysis.

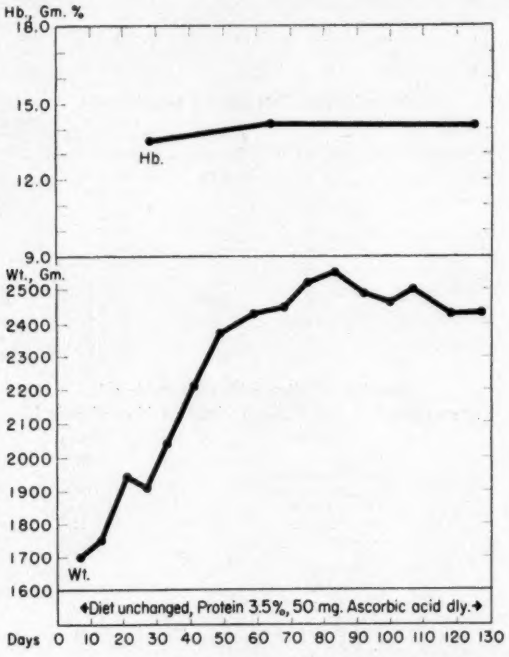

Chart 1.—Control monkey No. 67, fed Diet No. 4B (Table 1) and 50 mg. of ascorbic acid daily. The animal remained healthy, without anemia or abnormality in the marrow.

During their course they sometimes suffered brief bouts of diarrhea, which subsided spontaneously, or occasionally they were treated with aureomycin or sulfadiazine. We are not sure that this treatment was helpful or necessary. Dysentery bacilli were not found in a few cultures of the stools. A few animals tended to have loose stools all the time. It can certainly be stated that diarrhea was not an essential, outstanding, or consistent feature during the course of the monkeys in which megaloblastic anemia developed; they did not differ in this regard from the controls. No evidence of respiratory-tract infection was noted in any of this group of monkeys; if any was present, it must have been minimal.

Generally, but not invariably, diarrhea developed with the scurvy. Sometimes this was severe, bloody, and so dehydrating that fluids had to be given parenterally

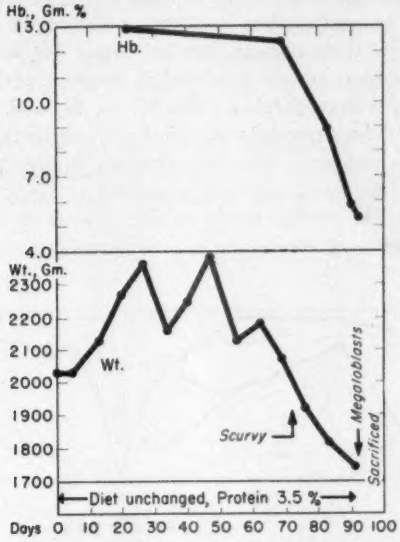

Chart 2.—Monkey No. 47, with experimental megaloblastic anemia, fed Diet No. 4B (Table 1) without ascorbic acid. The course was typical: scurvy in 70 days and megaloblastosis in 90 days. The animal was killed at the end of the study for tissue studies.

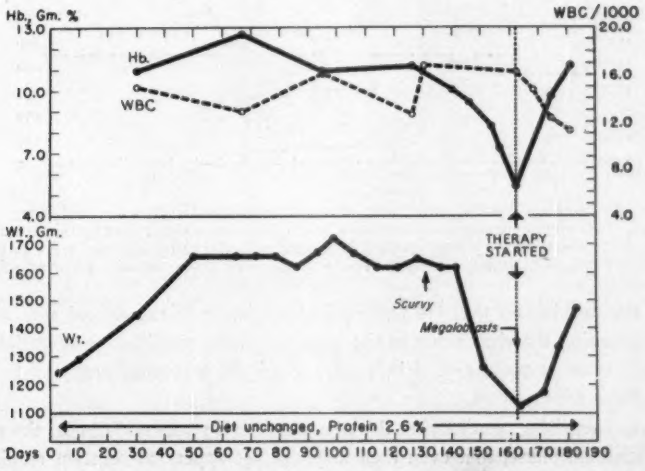

Chart 3.—Monkey No. 12, with experimental nutritional megaloblastic anemia, fed Diet No. 5 (Table 1). Ascorbic acid was not added to the diet, but small traces were found in the evaporated cow's milk in the diet; the onset of scurvy and megaloblastosis was delayed. The animal was treated with ascorbic acid and vitamin B_{12}. Vitamin B_{12} alone has no effect on this experimental megaloblastosis.

for a day or two. Consideration of this diarrhea is important, since one might be led to suppose this was essential to the development of the deficiencies causing megaloblastic anemia in these animals. We feel certain that such was not the case, first, because megaloblastic anemia developed in the same period in some animals that had never suffered from diarrhea (Nos. 47, 48, 49) and, second, because the diarrhea at this stage did not respond to antibiotics but soon ceased when an effective vitamin therapy was instituted. Diarrhea occurring in this terminal phase with scurvy and megaloblastic anemia might be considered as chiefly dependent upon the nutritional deficiency and possibly partly on the presence of offending organisms. In some instances diarrhea probably was not the cause but a complication or symp-

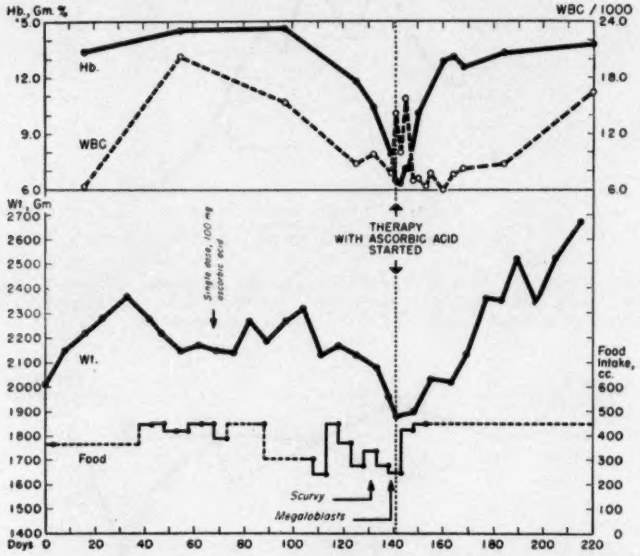

Chart 4.—Monkey No. 33, with experimental megaloblastic anemia, fed Diet No. 4B (Table 1). This monkey was given no ascorbic acid except for a single dose by mistake after two months. Note the temporary improvement in weight gain thereafter and the delay in the onset of scurvy and megaloblastosis. Complete recovery followed treatment with ascorbic acid alone.

tom of the deficiencies that led to megaloblastosis. It is not denied that frequent or long-standing diarrhea prior to the terminal phase could be an important conditioning factor in promoting deficiencies. Such did not usually appear to be the case in these experiments.

It was surprising, considering the emaciation and poor condition of the animals in this terminal phase, that even then they did not appear to contract respiratory-tract infections.

The fully developed characteristic megaloblastic changes in the marrow were usually found soon after scurvy appeared. Inspection of Table 2 and the graphs reveals that definite megaloblastosis was frequently discovered within two weeks

after scurvy. In one animal megaloblastosis developed 11 days before clinical scurvy (No. 50), and one was clearly scorbutic a month before megaloblastosis was fully developed (No. 24). Leukopenia was common in association with the megaloblastic marrow, but it was not consistently present. This variation in the relation between the onsets of scurvy and megaloblastosis is quite like the state of affairs in humans.

When the monkeys were fed the diets and supplements listed in Table 1, *without* ascorbic acid, megaloblastic anemia developed in every animal. If all the ascorbic acid in the diet was eliminated from the beginning of the experiment, the time

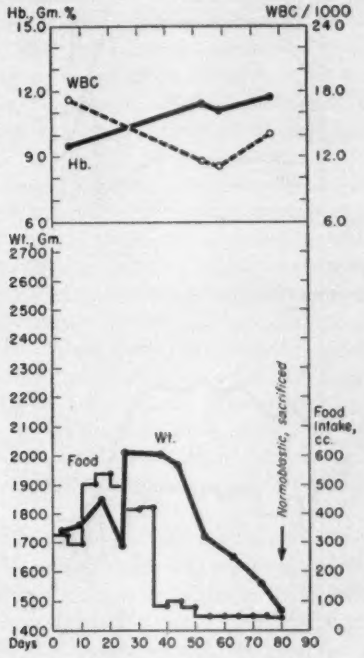

Chart 5.—Monkey No. 25, fed Diet No. 4 (Table 1) with 50 mg. of ascorbic acid daily. Severe restriction of food intake for a prolonged period produced marked weight loss but did not cause megaloblastosis or anemia. This monkey was killed for tissue studies.

required for the development of megaloblastic anemia was remarkably uniform, namely, about three months (Nos. 45, 47, 48, 49, 50, 51 in Table 2). When small amounts of ascorbic acid remained in the diet, the advent of megaloblastic anemia was greatly delayed, until the last trace of ascorbic acid was eliminated (animals Nos. 5 and 12A, Chart 3). One animal (No. 33, Chart 4), having been two months without ascorbic acid, received a single intramuscular injection of 100 mg. of ascorbic acid by mistake and then received no more. The appearance of megaloblastic anemia in this animal was delayed much longer than in others on the same

regimen (compare in Table 2 with Nos. 45, 47, 48, 49). In our experience with monkeys fed these diets without ascorbic acid, megaloblastosis invariably occurred within a month after clinical signs of scurvy appeared.

No differences were noted among the various types of milks used other than the tenacity with which a trace of ascorbic acid was preserved in some of them. Even the soy bean flour formula (Diet No. 8), which is much poorer in vitamin B_{12} than the milk diets, did not lead to exceptional results. Diet 4B has twice the protein content (3.5%) of diets 4 and 4A, but megaloblastic anemia occurred as

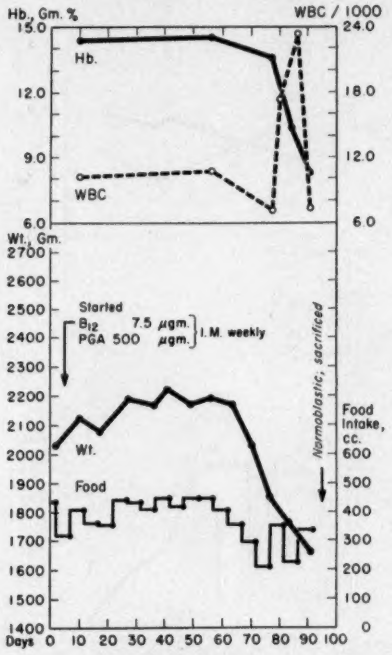

Chart 6.—Monkey No. 37, with scurvy without megaloblastic anemia, fed Diet No. 4B (Table 1). Ascorbic acid was not given. Although vitamin B_{12} and pteroylglutamic acid were both given prophylactically, anemia developed after hemorrhages due to scurvy which appeared on the 71st day. The marrow remained normoblastic. The animal was killed for tissue studies.

soon as and as regularly with diet 4B as with any other if ascorbic acid was not provided.

That simply a decrease in the food intake or severe inanition did not cause the megaloblastic anemia is shown by monkey No. 25 (Chart 5). This animal's food intake was reduced to one-tenth of what he had been eating. Twenty-five per cent of the body weight was lost during six weeks of underfeeding without the development of either anemia or megaloblastic changes in the marrow. The animal remained vigorous and lively and appeared entirely normal except for being thin.

MANIFESTATIONS IN THE BLOOD AND BONE MARROW

The changes in the megaloblastic marrows of the monkeys are virtually indistinguishable from those seen in pernicious and other megaloblastic anemias.[14] The marrow was hyperplastic as judged from hypercellularity of films made from aspirated marrow, and sections of marrow taken at autopsy from those animals that died at the height of megaloblastic anemia showed marked hyperplasia, the dominant cells being developing erythrocytes.

Megaloblasts varied considerably in relative numbers: counts between 50 and 60% were not unusual; two monkeys (Nos. 17 and 32) which were allowed to develop extreme megaloblastosis (77%) did not survive. Karyorrhexis, multiple Jolly bodies, and basophilic stippling were present in all megaloblastic marrows; karyolysis was usually, but not invariably, observed. Macrocytes (megalocytes) were reasonably numerous in some of the marrows, much less numerous in others. Some of the macrocytes, like those in megaloblastic anemia of man, were extremely large, being 20 μ or more in diameter. Only rarely could these gigantic macrocytes be found in the blood.

In all the megaloblastic marrows, developing neutrophils showed a marked increase in size and marked evidence of premature segmentation and hyperlobulation. The general pattern was frequently more striking than that ordinarily seen in human marrow. Increase in cell size and in nuclear lobulation was seen in eosinophils and basophils as well, but it was less uniformly present in these granulocytes than in the neutrophils.

In some of the marrows, megakaryocytes tended to show more bizarre nuclear contortions than do normal megakaryocytes. Also, multinucleated megakaryocytes were more numerous in the megaloblastic marrows than in the normal marrows. Abnormalities in cells of the megakaryocytic series were less uniform than those in developing erythrocytes and neutrophils. This finding is comparable to the erratic nature of the changes in megakaryocytes in pernicious and other megaloblastic anemias.

The alterations in the peripheral blood are also to be considered in more detail in the separate report regarding changes in the bone marrow.

The fact that there was a substantial drop in hemoglobin with megaloblastosis of the marrow is shown in Charts 2, 3, and 4. The progressive decrease in erythrocytes, often apparently not proportionately as great as one would expect in megaloblastic anemia, has been tabulated in appendix B.

Interpretation of changes in the peripheral blood has been difficult, and the fundamental changes might well be ignored or overlooked if only quantitative data were considered. Normal values[15] indicate that the erythrocyte of the monkey has a mean volume (67.5 cu. μ) approximately 25% less than that of the human erythrocyte, while the mean diameter (6.9 μ) is only 10% less. The average mean corpuscular hemoglobin concentration of 30.1% in the normal monkey is only slightly less than the average mean corpuscular hemoglobin concentration of the human erythrocyte. These data and the general appearance of the erythrocyte of

14. The morphology of the marrow has already been discussed by Sundberg [4] and illustrated in one of our other reports [12] and will be more fully considered in a separate communication.

15. Winkle, V. A.: The Study of Bone Marrow and Blood of Normal Laboratory Monkeys, Thesis, University of Minnesota, 1951, to be published.

the monkey indicate that it is a small, slightly pale, biconcave disk the maximum thickness of which is less than that of the human erythrocyte. The normal control monkeys had microcytic, slightly hypochromic erythrocytes if the cells are described with reference to normal human erythrocytes.

When megaloblastosis of the marrow was most pronounced, somewhat variable pictures were encountered. Often cell indexes showed the cells to be normocytic; sometimes macrocytosis was demonstrable even when there was no appreciable reticulocytosis, and least often the average mean corpuscular volumes were lower than control values. Corpuscular hemoglobin concentration was also variable, the levels ranging between those slightly below to those slightly above normal control values.

Of primary importance has been the fact that blood pictures comparable to those seen in pernicious and other megaloblastic anemias have been encountered in the megaloblastic monkeys.

The erythrocytes showed moderate anisocytosis and poikilocytosis. "Hyperchromatic" oval macrocytes were present in variable numbers. Polychromasia, in some animals at the height of megaloblastosis, was as minimal as that encountered in pernicious anemia. In others, polychromasia was moderate or even marked; increased polychromasia is unusual in pernicious anemia, but it has been observed in the megaloblastic anemia of infancy. Basophilic stippling was a prominent finding, and karyorrhexis and karyolysis as well as single and multiple Jolly bodies were also commonly present. In many of the instances in which nucleated erythrocytes were found in the circulating blood, the cells appeared to be normoblasts. Often the nucleated erythrocytes were larger than normal, and their cytoplasm frequently contained coarse basophilic stippling; many of these so-called normoblasts were comparable to the nucleated erythrocytes which can be found in the circulating blood in pernicious and other megaloblastic anemias. In addition to the latter cells (the identity of which has always been disputable), typical megaloblasts were also encountered in the blood. Moderate thrombocytopenia was apparent in some, but not all, of the blood films. The leukocyte count was generally low. Hypersegmented large neutrophils comparable to the pernicious anemia neutrophil were always present. In addition to the shift to the right in cells of the neutrophilic series, occasional giant neutrophil metamyelocytes with nuclei showing bizarre contortions were seen, and cells as young as neutrophil promyelocytes were not uncommon. In brief, it can be stated that although variable blood pictures have been encountered, some have been virtual replicas of the blood in pernicious anemia and megaloblastic anemia in infancy.

The one important difference has been the fact that even the "hyperchromatic" oval macrocytes have appeared thinner and less red-orange in color than the oval macrocytes seen in human blood from pernicious or other megaloblastic anemias. This difference was manifest even in the presence of quantitatively calculable macrocytosis (not based on increased reticulocytes) and normal or increased mean corpuscular hemoglobin concentration. Although the mean cell diameter reached levels seen in pernicious anemia and the mean corpuscular volume was increased over normal control values, the mean corpuscular volume never attained values as high as those expected in the human. The "hyperchromatic" oval macrocyte of the monkey is larger than the normal erythrocyte of the monkey, but it appears to be

thinner than the analagous "hyperchromatic" macrocyte of human blood. One is led to believe that this is probably a species difference.

In some of the monkeys, with megaloblastosis of the marrow, the blood picture showed the features characteristic of megaloblastic anemia, but, in addition, hypochromasia was more pronounced than in the erythrocytes of the normal monkey. In these animals, the serum iron and erythrocyte protoporphyrin levels were indicative of iron deficiency. Although the iron deficiency may be adequately explained by the scorbutic hemorrhage, some specific role of ascorbic acid has not been eliminated in these experiments.

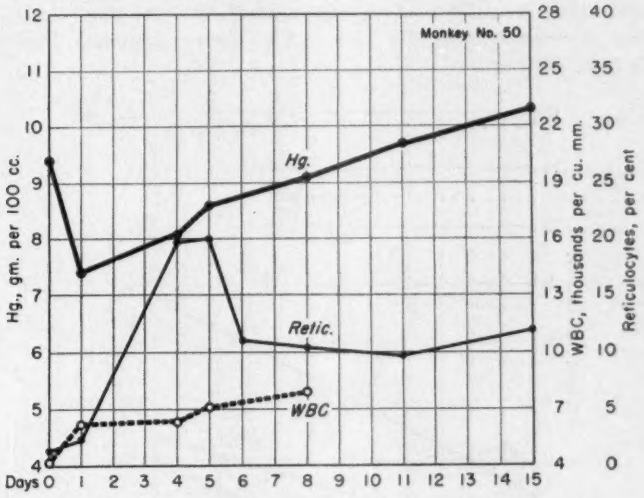

Chart 7.—Effect of synthetic folinic acid (50 γ of the crude substance, equivalent to 7.5 γ of "pure" folinic acid, intramuscularly daily) on the peripheral blood of a megaloblastic monkey.

RELATIONSHIPS OF PTEROYLGLUTAMIC ACID, FOLINIC ACID, VITAMIN B_{12}, AND ASCORBIC ACID TO THIS EXPERIMENTAL MEGALOBLASTIC ANEMIA

When the marrow was megaloblastic, the effects of certain compounds were determined. An animal was always continued on its experimental diet throughout the trial of any therapeutic agent. A comprehensive hematological evaluation of the effects of therapy will be reported separately, along with the further description of the blood and marrow referred to above. Here a summary account of the effects of therapy on the hematologic and the clinical features will be given.

Vitamin B_{12},[16] 15 γ daily intramuscularly, had no effect on the marrow, blood, or clinical symptoms (Nos. 14A, 17B).[12] In confirmation of this it was found that 7.5 γ of vitamin B_{12} intramuscularly given weekly as a supplement to the experimental diet did not prevent or delay the onset of this megaloblastic anemia or the usual clinical symptoms (Nos. 13B, 32).

16. Samples of vitamin B_{12} manufactured by Merck & Company, Inc., E. R. Squibb & Sons, and the Eli Lilly & Company have been used with the same results.

In sharp contrast, oral or intramuscular administration of pteroylglutamic acid [17] was followed by prompt disappearance of the megaloblastic pattern in the marrow (No. 24, Chart 8, and previous report [12]). Appetite improved, and diarrhea usually lessened or ceased. These effects were obtained without the aid of ascorbic acid, but unless this vitamin was added later the animal died of scurvy. Subsequent addition of ascorbic acid enabled animals to make a complete recovery. The megaloblastosis could be prevented by giving as little as 500 γ of pteroylglutamic acid weekly, orally or intramuscularly, even though severe scurvy developed and was endured for a month (Nos. 30, 39). Five micrograms added to the diet orally each day was not sufficient to prevent megaloblastosis (No. 14A).[12] Provision of the combined action of 7.5 γ of vitamin B_{12} and 500 γ of pteroylglutamic acid intramuscularly weekly gave the same, but no better, protection from megaloblastosis (No. 37).

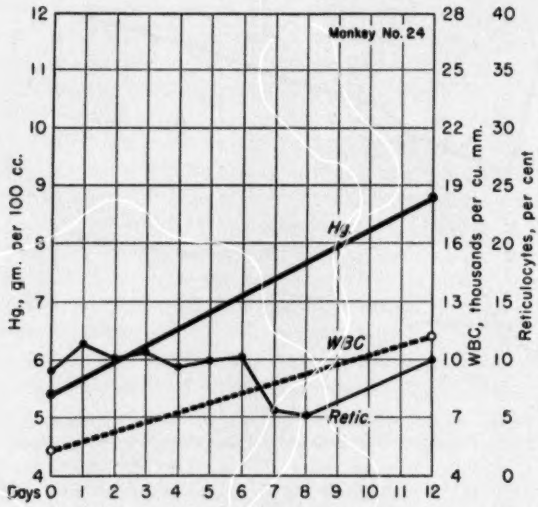
Monkey No. 24
Hg.
WBC
Retic.
Hg., gm. per 100 cc.
WBC, thousands per cu. mm.
Reticulocytes, per cent
Days
0 1 2 3 4 5 6 7 8 9 10 11 12
12 11 10 9 8 7 6 5 4
28 25 22 19 16 13 10 7 4
40 35 30 25 20 15 10 5 0

Chart 8.—Effect of pteroylglutamic acid (15 mg. intramuscularly daily) on the peripheral blood of a megaloblastic monkey.

Anemia, associated with a normoblastic marrow, did develop after symptoms of scurvy appeared during the prophylactic use of pteroylglutamic acid or persisted after treatment with pteroylglutamic acid even if vitamin B_{12} was also given (No. 37, Chart 6). This might be interpreted to indicate that there is an additional and specific function of ascorbic acid in hemopoiesis, but our data on pigment metabolism may be interpreted to indicate that this anemia is due to iron deficiency resulting from the hemorrhage characteristic of scurvy. With appearance of periorbital hemorrhages, the hemoglobin falls rapidly. The fecal urobilinogen becomes greatly increased, plasma iron decreases, and erythrocyte protoporphyrin increases. Complete data in this regard, which would lengthen this paper unduly, will be published separately.

17. Folvite,® Lederle Laboratories Division, American Cyanamid Company.

In another paper [12] we reported that a conjugate of pteroylglutamic acid, a pteroyltriglutamate,[18] was also effective even when given orally without ascorbic acid.

It is clear that deficiency of ascorbic acid itself is not the direct cause of the megaloblastosis; but, rather, deficiency of ascorbic acid leads to a deficiency of, or some disturbance in the metabolism of, pteroylglutamic acid. The megaloblastosis can be prevented or eliminated without ascorbic acid if sufficient pteroylglutamic acid is provded.

The smallest therapeutic dose of pteroylglutamic acid we have tried and found effective is 750 γ intramuscularly (No. 45); on one occasion 50 γ intramuscularly was ineffective (No. 32). In both of these experiments adequate vitamin B_{12}

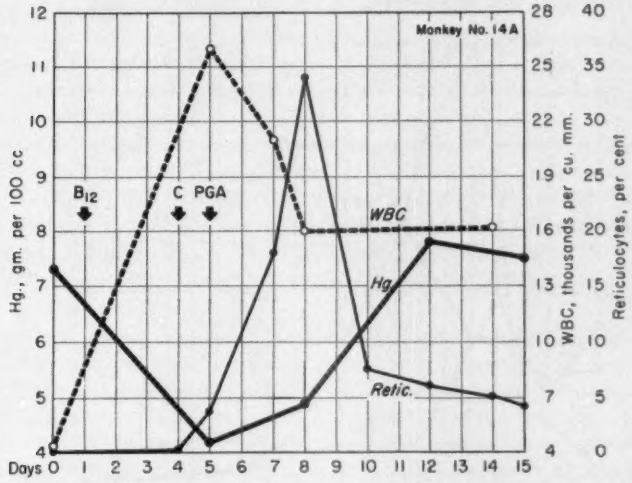
Monkey No. 14 A
B12
C PGA
WBC
Hg.
Retic.
Hg., gm. per 100 cc
WBC, thousands per cu. mm.
Reticulocytes, per cent
Days 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Chart 9.—Monkey No. 14, Period A, previously reported.[14] Vitamin B_{12} (15 γ intramuscularly), ascorbic acid (100 mg. intramuscularly), and pteroylglutamic acid (15 mg. intramuscularly) were given daily in rapid succession. This was an early experiment when the primary purpose was to demonstrate that the megaloblastosis and symptoms could be relieved by crystalline vitamins alone without change in the diet, i. e., to prove that protein deficiency was not responsible. This chart provides a basis for comparison in judging the effects when the vitamins were used separately.

was available because of prophylactic or simultaneous provision of supplementary vitamin B_{12}.

It is possible to eliminate the megaloblastic anemia and restore the animal to normal with ascorbic acid alone while the experimental diet (No. 33) is continued (Charts 4 and 10). Presumably ascorbic acid is effective because it permits reaccumulation of pteroylglutamic acid or restores its metabolism to normal.

Nichol and Welch have reported that ascorbic acid plays a role in enhancing production of folinic acid (Citrovorum factor) from pteroylglutamic acid.[19] We

18. Teropterin, Lederle Laboratories Division, American Cyanamid Company.

19. Nichol, C. A., and Welch, A. D.: Synthesis of Citrovorum Factor from Folic Acid by Liver Slices: Augmentation by Ascorbic Acid, Proc. Soc. Exper. Biol. & Med. **74**:52, 1950.

have found that folinic acid appears to be a more potent hemopoietic agent than pteroylglutamic acid in this experimental megaloblastic anemia.[20] Daily injection of 50 γ of a crude synthetic folinic acid,[21] estimated to contain 15%, or 7.5 γ, of folinic acid exerted as pronounced an effect on the blood, marrow, and symptoms in a scorbutic monkey with typical megaloblastic anemia (No. 50, Chart 7) as did 15 mg. of pteroylglutamic acid in a comparable animal (No. 24, Chart 8) or as did 750 micrograms of pteroylglutamic acid in another comparable animal (No. 45). This was confirmed in an animal with severer anemia (No. 51) with a slightly larger dose of another sample of synthetic folinic acid from the same source (estimated to provide a daily dose of 30 micrograms of folinic acid). As mentioned above 50 γ of pteroylglutamic acid was ineffective. Furthermore, administration of small doses of folinic acid before scurvy appeared prevented megaloblastosis in the marrow (No. 40B) just as effectively as did pteroylglutamic acid.

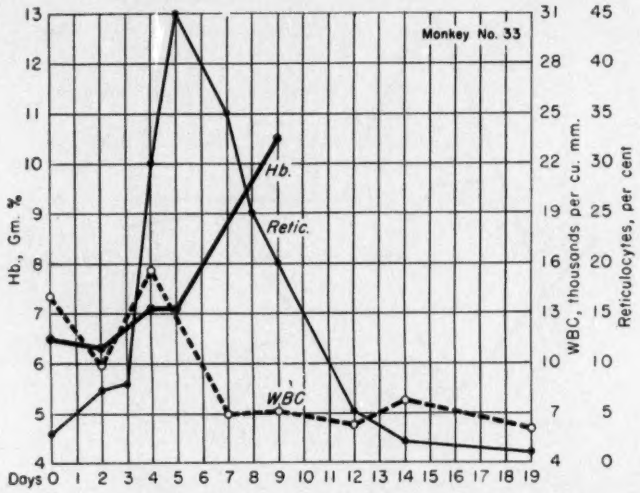

Chart 10.—Response in the peripheral blood of a megaloblastic monkey whose only treatment was intramuscular injection of 100 mg. of ascorbic acid daily.

These results would seem to be in keeping with the suggestion that ascorbic acid is required for the efficient conversion of pteroylglutamic acid to folinic acid. It must be kept in mind, however, that treatment with as little as 750 γ of pteroylglutamic acid produced prompt and pronounced effects without the aid of ascorbic acid (No. 45). The efficiency of scorbutic monkeys in producing folinic acid from pteroylglutamic acid will be studied.

As an incidental observation we have noted many times that aureomycin, being given to treat diarrhea, had no effect on the course of the megaloblastic pattern in the marrow.

20. May, C. D.; Sundberg, R. D., and Schaar, F.: Comparison of Effects of Folic Acid and Folinic Acids in Experimental Megaloblastic Anemia, J. Lab. & Clin. Med. **36**:963, 1950.

21. Provided by Dr. Edward Campbell, Director of Biochemical Research, The Eli Lilly Research Laboratories, where it was synthesized and assayed.

COMMENT

Megaloblastic anemia occurs regularly in monkeys fed milk diets deficient in ascorbic acid. These diets contain very little pteroylglutamic acid. Supplementing the diets with pteroylglutamic acid or folinic acid prevents or cures this megaloblastic anemia even in the presence of severe scurvy. Vitamin B_{12} alone will neither prevent nor cure this megaloblastic anemia while deficiency of ascorbic acid remains.

These facts indicate that this megaloblastic anemia is a result of a deficiency of pteroylglutamic acid or its metabolic products. The means by which ascorbic acid exerts its influence on pteroylglutamic acid metabolism in these experiments has not been determined definitely. Nichol and Welch have suggested the ascorbic acid facilitates the conversion of pteroylglutamic acid to folinic acid. We have presented data that indicate that folinic acid may be more potent than petroylglutamic acid in restoring this megaloblastic marrow to normal.

There is no indication that deficiency of vitamin B_{12} played a role in the pathogenesis of megaloblastosis in these animals. The soy-bean-flour diet No. 8, which is particularly low in vitamin B_{12}, gave results similar to those obtained with milk diets.

Clear evidence has been presented that ascorbic acid deficiency did not merely cause anorexia and reduced intake of food or make the animals susceptible to infections or diarrhea, which, in turn, might cause a deficiency of pteroylglutamic acid. The involvement of ascorbic acid seems subtler than that. Johnson and Dana,[22] Dietrich and associates,[23] and Woodruff and associates[24] have also reported experiments indicating an interrelation between ascorbic acid and pteroylglutamic acid.

It has been pointed out that in none of the control animals did megaloblastic anemia develop on these diets when they were supplemented with ascorbic acid during the control periods, i. e., in the time required to produce megaloblastic marrows in animals fed these diets without ascorbic acid. One of the control animals (No. 7) was continued on milk diets and ascorbic acid after a typical megaloblastic marrow had developed in the animal not receiving ascorbic acid (No. 5) for which it was a control. Megaloblastic anemia developed in 311 days in the scorbutic animal (No. 5). Fifty-eight days later, when the control (No. 7) had been on milk diets with adequate ascorbic acid for 388 days, symptoms suddenly developed and a megaloblastic marrow was found.

A similar event occurred in the case of monkeys No. 9 and No. 10 previously reported on in part.[12] No. 9 had two episodes of megaloblastosis in a period of 235 days, 123 and 108 days after ascorbic-acid administration was discontinued in experimental periods A and B respectively. Thirty-three days after the second episode of megaloblastosis in No. 9, megaloblastosis finally developed in the control animal (No. 10) also, after it had been on the milk diet with ascorbic acid for 269

22. Johnson, B. C., and Dana, A. S.: Ascorbic Acid Therapy of Pteroylglutamic Acid-Deficient Rats, Science **108**:210, 1948.

23. Dietrich, L. S.; Nichol, C. A.; Monson, W. J., and Elvehjem, C. A.: Observations on the Interrelation of Vitamin B_{12}, Folic Acid, and Vitamin C in the Chick, J. Biol. Chem. **181**:915, 1949.

24. Woodruff, C. W.; Cherrington, M. E.; Stockell, A. K., and Darby, W. J.: The Effect of Pteroylglutamic Acid and Related Compounds Upon Tyrosine Metabolism in the Scorbutic Guinea Pig, J. Biol. Chem. **178**:861, 1949.

days. No cause could be found at autopsy of these animals, No. 7 and No. 10, to account for their development of megaloblastosis. It is conceivable that these milk diets, providing only about 2 γ of pteroylglutamic acid a day to the animals, may be only barely adequate in this vitamin. Perhaps in monkeys kept long enough on such diets, even with adequate ascorbic acid, megaloblastic anemia would occasionally develop. We are collecting data on this possibility. Monkey No. 4 has been fed milk diets for 973 days (since birth) without megaloblastosis. Its blood remains normal. One might take the point of view that ascorbic-acid deficiency favors a tendency toward pteroylglutamic-acid deficiency in monkeys fed these milk diets. Ascorbic acid certainly delays the development of megaloblastic anemia or pteroylglutamic-acid deficiency in these circumstances, since, without ascorbic acid, megaloblastosis developed regularly in 70 to 116 days (Table 2). With adequate ascorbic acid megaloblastosis appeared in No. 7 and No. 10 only after 269 days. The implications of this for human infant nutrition have been discussed.[12]

As to the role of infection in our experiments, we have already commented upon diarrhea and the absence of symptoms of respiratory-tract infections. Study of the gross and microscopic pathology of the animals which were killed or died did not reveal any evidence of either respiratory or generalized infection. No pathologic changes other than those attributable to scurvy were found in some of the animals. Occasionally a diffuse mild to moderate colitis of an inflammatory type was noted. Sometimes small, well-localized areas of inflammatory reaction around worms embedded in the wall of the large bowel were seen. It seems fair and reasonable to assert that infection was not a prominent or consistent finding, either clinically or pathologically, in the animals in which megaloblastosis developed.

Infection, identified only by microscopic examination, was probably not very significant, since the course of the affected animals was no different from that of animals without any evidence of infection.

These comments are included to indicate that they have been given due consideration in the drawing of conclusions from the experimental observations.

CONCLUSIONS

1. Megaloblastic anemia has been produced regularly in monkeys by feeding milk diets deficient in ascorbic acid.

2. Monkeys fed the same milk diets supplemented with adequate ascorbic acid remain in good health for prolonged periods and maintain normal blood and bone marrow.

3. This experimental megaloblastosis is virtually indistinguishable from that seen in megaloblastic anemia in humans, particularly the form encountered most frequently in infancy.

4. This experimental megaloblastosis can be eliminated or prevented by pteroylglutamic acid or folinic acid without the aid of ascorbic acid. It can also be cured by ascorbic acid alone. Vitamin B_{12} will neither cure nor prevent it.

5. This experimental megaloblastosis is due to a disturbance in the metabolism of pteroylglutamic acid caused by a deficiency of ascorbic acid.

6. Application of this knowledge to elucidation of the pathogenesis of megaloblastic anemia in infancy is mentioned.

APPENDIX A

Regimen Currently Employed for Producing Megaloblastic Anemia

Animals.—Approximately 2 kg. immature rhesus monkeys from animal dealer. Each given 100 mg. ascorbic acid intramuscularly and tuberculin tested. Keep in individual cages if possible.

Diet.—Whole dried cows milk, 12 gm;. water, 100 cc.; 5% $CuSO_4$, 1 drop. Store in cold overnight; boil for five minutes before feeding. Offer 50 to 75 cc. per kilogram in the morning and 100 to 150 cc. per kilogram in the afternoon, adjusting according to appetite.

Supplements.—Vitamin A, 2,000 I. U., and Vitamin D, 200 I. U., in a water-miscible preparation, in the morning feeding.

Iron as ferrous compound in a water-soluble form to provide 25 mg. ferrous iron a day. Given in the afternoon feeding.

B vitamins: Once a week, intramuscular injection of thiamine hydrochloride, 5 mg.; riboflavin, 2 mg.; nicotinamide, 75 mg.; sodium panthotenate, 2.5 mg.; pyridoxine hydrochloride, 5 mg.

Ascorbic acid, used in control animals only, 50 mg. daily in the morning feeding and 50 mg. intramuscularly once a week, or a 50 mg. tablet of ascorbic acid may be handed to the animal directly as they will usually grab it and eat it eagerly.

APPENDIX B

Data from the protocols of the experimental animals. Intakes given in the tables are average for the preceding five days. In a few instances some of the data were collected a day or two removed from the actual date indicated; whenever it made no difference such data were grouped under a single day in order to save space. When there were long uneventful periods, only representative data are given rather than all the data which were obtained. The values for leukocytes as given are corrected for the presence of nucleated erythrocytes, which were so numerous in the peripheral blood at times that uncorrected leukocyte counts would be very misleading. The actual number of nucleated erythrocytes per cubic millimeter is listed also in the parenthesis following the corrected leukocyte count.

Monkey No. 4A, C, E, Cynomolgus, male
Control: Diets No. 4, 4B, 5 with ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
Period A										
0	6/20/48	.....	...	.....	....	....	..	...	...	Taken from mother at birth and placed on Diet No. 5
57	8/16/48	0.501	...	.....	4.84	9.0	..	0.8	...	.....
73	9/ 1/48	0.650	...	6,700	4.74	9.3	..	0.6	N.*	.....
137	11/ 4/48	0.830	...	17,200	6.66	12.1	..	...	N.	.....
165	12/ 2/48	0.990	...	17,600	7.54	14.3	..	...	N.	Period B (3/11/49 to 7/26/49); diet changed to No. 2 previous report
204	3/11/49	1.390	...	.....	5.35	9.0	..	0.3	N.	.....
Period C										
0	7/26/49	1.54	360	12,000	6.11	10.9	44	0.3	N.	Diet changed to No. 4
45	9/ 9/49	1.68	220	5,350	6.12	11.0	..	0.2	...	Acute diarrhea and anorexia 1 wk.
100	11/ 3/49	1.98	340	20,250	6.28	10.8	45	0.0	N.	Period D (12/20/49 to 3/7/50); diet changed to 4A supplemented with B_{12} and P.G.A.†; course not remarkably different
147	12/20/49	2.04	420	14,300	6.87	9.7	40	...	...	.....
Period E										
0	3/ 7/50	2.22	420	8,450	6.93	11.7	40	0.8	N.	Diet changed to No. 4B
69	5/15/50	2.48	500	16,250	6.22	12.1	43	0.4	N.	.....
120	7/ 5/50	2.45	530	16,150	7.12	12.1	41	0.5	N.	.....
150	8/ 4/50	2.51	450	10,950	6.25	11.4	41	...	N.	.....
183	9/ 6/50	2.42	...	11,500	6.09	8.9	35	8.4	N.	.....
220	10/13/50	2.44	...	11,500	5.14	11.7	46	1.0	N.	.....
272	12/ 4/50	2.57	...	18,700	6.22	12.3	44	0.6	N.	.....
348	2/20/51	2.89	...	19,300	6.95	11.4	44	0.6	N.	.....

Summary: The animal has lived on milk diets since birth, 973 days, without megaloblastosis.

Monkey No. 5, rhesus, male, wt. 2.61 Kg.
Diets No. 4 and No. 4A; no ascorbic acid; killed when megaloblastic for tissue analyses

Day	Date	Wt., Kg.	Intake, Cc.	Leuko-cytes	Erythro-cytes, Millions	Hemo-globin, Gm./ 100 Cc.	Hema-tocrit	Reticu-locytes per 100 RBC.	Marrow	Comments
1	3/11/49	2.61	...	.....	....	....	..	...	...	Diet No. 4; no ascorbic acid
10	3/21/49	2.71	440	.....	....	....	..	...	...	.....
14	3/25/49	....	410	10,300	5.98	11.9	42	0.2	N.	.....
45	4/25/49	2.74	450	.....	....	....	..	...	...	.....
65	5/15/49	3.14	575	.....	....	....	..	...	...	.....
78	5/28/49	....	520	20,600	5.15	11.3	38	0.9	N.	.....
84	6/ 4/49	3.00	555	.....	....	....	..	...	...	.....
97	6/16/49	....	550	16,400	5.40	11.4	46	1.8	...	.....
129	7/18/49	2.99	600	12,000	5.50	11.8	43	1.0	N.	.....
160	8/18/49	3.04	460	13,900	6.30	12.2	45	0.9	...	.....
182	9/ 9/49	2.76	480	8,500	6.73	12.6	..	0.5	...	.....
217	10/14/49	3.12	460	12,400	6.50	13.5	46	0.6	...	.....
244	11/10/49	3.22	490	.....	....	....	..	...	N.	.....
273	12/ 9/49	3.12	425	9,400	6.25	12.5	46	0.1	...	Diet No. 4A
307	1/12/50	2.92	200	4,500	6.22	11.6	43	...	M.‡	Gingival hemorrhage—scurvy
311	1/16/50	2.62	160	4,450	5.83	11.1	42	...	M.	Killed for tissue analyses

Summary: The animal remained in good health until near end of experiment. The feces tended to be loose at first but finally were formed. Diarrhea recurred only with signs of scurvy and megaloblastosis. Scurvy was greatly delayed until the last trace of ascorbic acid in milk was destroyed by copper sulfate and boiling. Other animals on the same diet with copper sulfate treatment from the start showed scurvy and megaloblastosis within 100 days.

Monkey No. 7, rhesus, male, wt. 2.02 Kg.
Control; Diets No. 4 and No. 4A with ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leuko-cytes	Erythro-cytes, Millions	Hemo-globin, Gm./ 100 Cc.	Hema-tocrit	Reticu-locytes per 100 RBC.	Marrow	Comments
0	3/ 7/49	2.02	...	.....	....	....	..	...	...	Started on Diet No. 4
18	3/25/49	2.01	500	7,100	5.53	10.5	36	0.7	N.	.....
64	5/10/49	2.59	395	18,600	6.37	9.9	43	0.6	...	.....
101	6/16/49	2.44	450	14,500	5.45	9.6	42	1.2	...	.....
133	7/18/49	2.37	475	13,500	6.08	10.5	44	0.4	N.	.....
164	8/18/49	2.37	400	15,400	6.52	10.8	46	0.1	...	.....
225	10/18/49	2.62	555	11,500	6.30	10.1	42	0.4	N.	.....
288	12/20/49	2.72	470	14,200	6.04	10.8	42	...	...	Diet changed to No. 4A
357	2/27/50	2.65	300	11,350	4.68	10.7	38	0.8	...	Diet No. 2, 1/31/50 to 2/23/50; diet No. 4B till death
378	3/20/50	2.62	385	10,050	5.11	11.2	37	0.5	N.	.....
388	3/30/50	2.18	...	1,400	6.35	13.9	45	0.6	M.	Dehydrated; died suddenly

Summary: The animal remained in good health as control for No. 5, on same diets, until after No. 5 showed megaloblastosis. No. 7 showed megaloblastosis 58 days after No. 5. A full account is given in the text.

Monkey No. 12A, rhesus, male, wt. 1.24 Kg.
Diet No. 5 without ascorbic aid; treatment of megaloblastosis with vitamin B_{12} and ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leuko-cytes	Erythro-cytes, Millions	Hemo-globin, Gm./ 100 Cc.	Hema-tocrit	Reticu-locytes per 100 RBC.	Marrow	Comments
0	4/15/49	1.24	...	.....	....	....	..	...	...	Started on Diet No. 5
30	5/15/49	1.44	275	15,000	6.29	11.0	..	0.4	N.	.....
67	6/21/49	1.67	325	13,300	6.18	12.6	46	0.5	...	.....
95	7/19/49	1.67	300	16,200	5.76	11.0	43	0.7	N.	Diet boiled after 7/26/49
126	8/19/49	1.65	250	12,900	6.83	11.4	44	0.5	...	Periorbital hemorrhages; scurvy on 8/23/49
140	9/ 2/49	1.62	120	17,400	5.31	10.1	37	1.3	N.	9/13/49 to 9/24/49, bloody diarrhea unrelieved by aureomycin
157	9/19/49	1.19	110	17,500 (500)	3.77	7.3	28	3.0	M.	.....
162	9/24/49	1.12	170	.....	2.80	5.5	22	10.2	M.	15 γ B_{12} + 100 mg. ascorbic acid I.M. on 9/24/49 and 9/25/49
164	9/26/49	....	100	.....	....	....	..	10.3	...	.....
165	9/27/49	....	...	15,400 (15,600)	....	....	..	11.7	...	Marked improvement; diarrhea subsiding
166	9/28/49	....	...	.....	....	....	..	12.4	...	.....
167	9/29/49	....	...	.....	....	....	..	10.1	N.	.....
168	9/30/49	....	330	12,450 (1,350)	....	....	..	8.0	...	Stools formed; behavior normal
171	10/ 3/49	1.22	...	.....	....	....	..	5.5	...	.....
173	10/ 5/49	....	...	12,300 (100)	4.80	9.9	42	4.3	...	15 mg. P.G.A. I.M.
174	10/ 6/49	....	350	.....	....	....	..	1.6	N.	15 mg. P.G.A. I.M.
175	10/ 7/49	....	...	.....	....	....	..	1.8	...	.....
177	10/ 9/49	1.33	...	.....	....	....	..	0.5	...	.....
178	10/10/49	....	...	.....	....	....	..	0.5	N.	.....
179	10/11/49	....	335	.....	....	....	..	0.3	...	.....
181	10/13/49	....	...	11,200	....	11.1	..	0.7	...	.....
182	10/14/49	1.47	400	.....	5.35	....	44	0.7	...	.....

Summary: Advent of scurvy and megaloblastosis delayed until last trace of ascorbic acid was removed from evaporated milk by boiling. Response to B_{12} plus ascorbic acid was prompt and complete. There was no added effect from P.G.A. The response was no greater than can occur with ascorbic acid alone (compare with No. 33). Diarrhea and megaloblastic marrow were unaffected by aureomycin but were promptly relieved by vitamin therapy.

Monkey No. 13B, rhesus, female, wt. 1.83 Kg.
Vitamin B_{12} given prophylactically; Diet No. 4; no ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	9/ 6/49	1.83	...	.....	....	....	..	...	N.	Diet No. 4 started
13	9/19/49	1.90	510	16,500	6.39	12.0	47	0.1	...	.....
22	9/28/49	1.90	465	.....	....	....	..	...	...	15 γ vitamin B_{12} I.M.
36	10/12/49	....	...	.....	....	....	..	...	...	15 γ vitamin B_{12} I.M.
53	10/29/49	2.08	450	.....	....	....	..	...	...	15 γ vitamin B_{12} I.M.
58	11/ 3/49	....	...	11,600	5.25	10.5	42	0.5	...	.....
73	11/18/49	2.08	200	.....	....	....	..	...	N.	15 γ vitamin B_{12} I.M.
86	12/ 1/49	....	310	.....	....	....	..	...	...	15 γ vitamin B_{12} I.M.
90	12/ 5/49	1.85	100	6,050 (200)	....	13.5	51	0.7	M.	Scurvy; bloody diarrhea; dehydrated; penicillin and aureomycin no effect
91	12/ 6/49	....	...	.....	....	....	..	...	...	Died

Summary: Vitamin B_{12} did not prevent megaloblastosis in the presence of scurvy. Aureomycin had no effect on diarrhea or megaloblastic marrow. There was anorexia for one month before megaloblastosis. Also note B_{12} did not prevent leukopenia.

Monkey No. 14B, rhesus, male, wt. 2.15 Kg.
P. G. A. given prophylactically; Diet No. 4 and 4A; no ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	9/ 6/49	2.15	...	.....	....	....	..	...	...	Diet No. 4 started
6	9/12/49	2.12	430	17,200	6.12	11.7	..	0.3	N.	.....
15	9/21/49	....	535	.....	....	....	..	...	...	15 mg. P.G.A. I.M.
24	9/30/49	....	485	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
32	10/ 8/49	2.28	495	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
39	10/15/49	....	440	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
42	10/18/49	2.31	575	12,800	5.71	11.1	43	0.1	N.	.....
45	10/21/49	2.22	470	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
53	10/29/49	2.22	340	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
62	11/ 7/49	2.17	340	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
69	11/14/49	2.22	230	.....	....	....	..	...	N.	5 mg. P.G.A. P.O.
83	11/28/49	2.17	220	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
89	12/ 4/49	2.08	250	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
97	12/12/49	2.12	190	.....	....	....	..	...	...	5 mg. P.G.A. P.O.
103	12/18/49	1.97	230	12,400	5.72	11.1	41	...	...	5 mg. P.G.A. P.O.
104	12/19/49	....	...	.....	....	....	..	...	N.	Periorbital hemorrhage; scurvy
105	12/20/49	....	...	.....	....	....	..	...	...	Diet changed to No. 4A
106	12/21/49	....	...	15,200	....	10.6	..	...	...	5 mg. P.G.A. P.O. by gavage
108	12/23/49	1.94	310	21,100 (1,400)	5.19	8.4	32	...	N.	5 mg. P.G.A. P.O. by gavage
110	12/25/49	....	...	.....	....	....	..	...	...	5 mg. P.G.A. P.O. by gavage
112	12/27/49	....	...	.....	....	....	..	...	N.	5 mg. P.G.A. P.O. by gavage
114	12/29/49	....	...	.....	....	....	..	...	...	5 mg. P.G.A. P.O. by gavage
115	12/30/49	....	205	2,100 (3,700)	4.17	7.2	..	...	N.	.....
116	12/31/49	....	...	.....	....	....	..	...	...	5 mg. P.G.A. P.O. by gavage
117	1/ 1/50	....	...	.....	....	....	..	...	...	5 mg. P.G.A. P.O. by gavage
119	1/ 3/50	1.81	...	4,500 (2,050)	2.75	5.6	22	10.8	N.	15 mg. P.G.A. I.M.
120	1/ 4/50	....	140	.....	....	....	..	...	...	5 mg. P.G.A. P.O. by gavage
121	1/ 5/50	....	...	.....	....	....	..	...	...	Killed for tissue analyses; gross hematuria terminally

Summary: P.G.A. prevented megaloblastosis. There was anemia with normoblastic marrow associated with the severe scurvy which developed.

Monkey No. 23, rhesus, male, wt. 2.26 Kg.
Control; Diet No. 7 with ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	11/28/49	2.26	...	.....	....	....	..	...	...	Diet No. 7 started
18	12/16/49	2.37	420	14,500	6.02	13.0	47	...	...	.....
91	2/27/50	2.31	330	7,700	6.30	14.0	43	...	...	.....
119	3/27/50	2.44	400	7,550	6.80	13.2	41	...	N.	.....
133	4/10/50	2.56	480	8,400	5.79	14.0	43	...	...	.....
154	5/ 1/50	2.53	485	11,850	6.68	14.3	43	...	N.	.....
177	5/24/50	2.59	500	7,950	6.96	14.9	..	...	N.	Killed for tissue analyses

Summary: Uneventful course. The corresponding animal without ascorbic acid showed megaloblastosis in 119 days.

Monkey No. 24, rhesus, male, wt. 2.01 Kg.

Diet No. 7; no ascorbic acid; treatment of megaloblastosis with large doses of P. G. A.

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	11/28/49	....	...	.....	....	....	..	...	...	Diet No. 7 started
28	12/26/49	2.17	380	17,000	6.17	12.5	43	...	N.	.....
63	1/29/50	2.10	370	.....	....	....	..	...	...	.....
88	2/24/50	1.97	190	14,600	5.68	12.5	39	0.6	...	Scurvy, periorbital hemorrhage on 2/26/50
106	3/14/50	1.76	245	19,100 (100)	5.05	11.7	39	1.5	...	.....
114	3/22/50	1.67	305	18,000 (200)	4.28	8.9	26	1.5	...	Loose bloody feces
119	3/27/50	....	160	5,850 (50)	2.75	6.5	22	4.2	M	.....
121	3/29/50	1.4	165	.....	....	5.4	..	9.0	...	15 mg. P.G.A. I.M.
122	3/30/50	....	...	.....	....	....	..	11.3	...	15 mg. P.G.A. I.M.
123	3/31/50	....	...	.....	....	....	..	10.1	...	15 mg. P.G.A. I.M.
124	4/ 1/50	....	...	.....	....	....	..	10.7	...	15 mg. P.G.A. I.M.
125	4/ 2/50	....	...	.....	....	....	..	9.4	N.	15 mg. P.G.A. I.M.; feces improving
126	4/ 3/50	....	...	.....	....	....	..	9.9	...	15 mg. P.G.A. I.M.
127	4/ 4/50	....	200	.....	....	....	..	10.3	...	15 mg. P.G.A. I.M.
128	4/ 5/50	....	...	.....	....	....	..	5.6	...	15 mg. P.G.A. I.M.
129	4/ 6/50	....	...	.....	....	....	..	5.2	...	15 mg. P.G.A. I.M.; no diarrhea
133	4/10/50	1.24	200	11,250	3.48	8.8	31	10.0	N.	15 mg. P.G.A. I.M.; no diarrhea

Summary: Diarrhea first appeared simultaneously with development of megaloblastosis and was relieved by P.G.A. without aid of antibiotics. The animal died of scurvy. Note rapid fall of hemoglobin after onset of scurvy and at a time of megaloblastosis.

Monkey No. 25, rhesus, male, wt. 1.74 Kg.

Starvation experiment; Diet No. 4 with ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	11/25/49	1.74	...	.....	....	....	..	...	...	Diet No. 4 started
6	12/ 1/49	....	325	17,200	4.94	9.5	35	...	N.	.....
36	12/31/49	2.10	420	.....	....	....	..	...	...	Diet intake restricted to 100 cc.; water ad lib.
42	1/12/50	1.97	100	.....	....	....	..	...	...	Diet intake restricted to 50 cc.; water ad lib.
53	1/17/50	1.72	50	11,600	6.08	11.4	44	...	N.	.....
59	1/23/50	1.65	50	11,100	6.28	11.1	42	...	...	.....
77	2/10/50	....	50	14,100	6.02	11.7	41	...	N.	.....
80	2/13/50	1.47	50	.....	....	....	..	...	...	Killed for tissue analyses

Summary: The animal remained lively and hungry throughout experiment.

Monkey No. 30, rhesus, male, wt. 1.81 Kg.

P. G. A. given prophylactically, 500 γ I. M. weekly; Diet 4B; no ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
52	1/19/50 to	1.81	...	.....	....	....	..	...	...	Preliminary period on milk diets
	3/12/50	2.15	450	.....	....	....	..	...	...	with ascorbic acid
53	3/13/50	....	...	.....	....	....	..	...	...	Ascorbic acid discontinued and Diet 4B started
58	3/18/50	....	...	.....	....	....	..	...	...	500 γ P.G.A. I.M. weekly started
63	3/23/50	2.19	450	6,850	5.03	12.8	40	1.1	N.	.....
102	5/ 1/50	2.19	420	15,450	6.70	13.6	42	0.5	N.	.....
129	5/29/50	1.95	230	13,650	....	12.3	..	0.9	N.	Scurvy
137	6/ 5/50	1.85	200	.....	....	9.8	..	...	...	Feces loose for first time
146	6/14/50	1.64	280	19,750 (200)	4.22	8.0	21	12.2	...	.....
151	6/19/50	1.49	350	11,000 (250)	3.48	6.2	21	15.0	N.	Diarrhea mild
153	6/21/50	....	...	.....	....	....	..	...	...	Killed for tissue analysis

Summary: P.G.A. prevented megaloblastosis but not anemia in the face of severe prolonged scurvy. There were marked anorexia and mild diarrhea. No antibiotics were used.

Monkey No. 32, rhesus, male, wt. 1.94 Kg.

Vitamin B_{12} given prophylactically; Diet No. 4B; no ascorbic acid; treatment of megaloblastosis with a small dose of P. G. A.

Day	Date	Wt., Kg.	Intake, Cc.	Leuko-cytes	Erythro-cytes, Millions	Hemo-globin, Gm./ 100 Cc.	Hema-tocrit	Reticu-locytes per 100 RBC.	Marrow	Comments
47	1/19/50 to	1.94	...	.....	....	....	..	...	...	Preliminary period on milk diets
	3/ 7/50	2.17	420	.....	....	....	..	...	...	with ascorbic acid
59	3/19/50	....	...	8,600	6.04	12.6	43	0.8	N.	Ascorbic acid discontinued; on Diet 4B since 3/7/50
86	4/15/50	2.28	375	.....	....	....	..	...	...	Vitamin B_{12}, 7.5 γ I.M. weekly started
109	5/ 8/50	2.03	450	4,850 (50)	7.04	12.5	41	1.3	M.	Eating well; no diarrhea
116	5/15/50	1.96	301	.....	....	11.1	34	0.9	M.	Sudden anorexia and diarrhea; aureomycin, 250 mg. daily
120	5/19/50	....	270	3,800 (500)	3.7	9.0	30	1.3	M.	No clinical signs of scurvy
121	5/20/50	....	...	.....	....	....	..	...	M.	50 γ P.G.A. I.M.
122	5/21/50	....	...	5,400 (4,100)	....	6.7	..	1.9	...	Died

Summary: Vitamin B_{12} did not prevent development of megaloblastosis or anemia. The megaloblastic marrow was not altered by aureomycin. Megaloblastosis preceded the onset of diarrhea, which was also unaffected by aureomycin.

Monkey No. 33, rhesus, female, wt. 1.47 Kg.

Diet No. 4B; no ascorbic acid; treatment of megaloblastosis with ascorbic acid alone

Day	Date	Wt., Kg.	Intake, Cc.	Leuko-cytes	Erythro-cytes, Millions	Hemo-globin, Gm./ 100 Cc.	Hema-tocrit	Reticu-locytes per 100 RBC.	Marrow	Comments
47	1/19/50 to	....	...	.....	....	....	..	...	...	Preliminary period on milk diets
	3/ 7/50	1.47	355	9,400	5.02	12.5	40	0.5	N.	with ascorbic acid
59	3/19/50	2.01	...	.....	....	....	..	...	...	Ascorbic acid discontinued
63	3/23/50	2.22	...	6,350	5.90	13.4	43	0.9	N.	On Diet No. 4B since 3/7/50
102	5/ 1/50	2.15	420	20,500	6.99	14.5	46	0.5	N.	.....
115	5/14/50	2.15	...	.....	....	....	..	...	...	Ascorbic acid 100 mg. I.M. by mistake
144	6/12/50	2.27	...	15,350	6.18	14.6	42	0.6	N.	Ate well and no diarrhea
158	6/23/50 to	....	...	.....	....	....	..	...	N.	Bloody (scurvy?) diarrhea; aureo-
	6/26/50	2.17	240	.....	....	....	..	...	...	mycin, 250 mg. daily, without improvement
172	7/10/50	....	...	8,700	5.78	11.8	38	2.2	...	Mild diarrhea continued
178	7/16/50	2.08	275	9,650 (100)	4.47	10.4	34	2.8	M.	Definite scurvy, periorbital hemorrhage
186	7/24/50	1.96	280	7,550 (200)	3.59	7.9	26	2.1	M.	Diarrhea severer; very inactive
188	7/26/50	1.88	...	13,750 (400)	....	6.5	22	3.0	M.	100 mg. ascorbic acid I.M.
189	7/27/50	....	...	.....	....	....	..	...	...	100 mg. ascorbic acid I.M.
190	7/28/50	....	245	8,950 (1,000)	2.70	6.3	20	7.3	...	100 mg. ascorbic acid I.M.
191	7/29/50	....	...	.....	....	....	..	8.0	...	50 mg. ascorbic acid P.O. daily
192	7/30/50	....	...	6,900 (8,800)	....	7.1	..	30.0	...	Ate better
193	7/31/50	....	...	.....	....	7.1	..	45.0	N.	Diarrhea gradually subsided
195	8/ 2/50	1.90	425	5,950 (900)	....	....	..	35.0	...	.....
196	8/ 3/50	....	...	.....	....	....	..	25.0	...	.....
197	8/ 4/50	....	...	7,150	4.16	10.5	31	20.0	...	.....
200	8/ 7/50	....	450	6,300	....	....	..	5.1	N.	8/6/50, 8/7/50, 100 mg. ascorbic acid I.M
202	8/ 9/50	2.03	...	7,700	....	....	..	2.1	...	Feces semiformed
207	8/14/50	....	...	5,800	....	12.9	43	1.1	...	Feces formed
211	8/18/50	2.02	...	7,650	5.56	13.1	42	0.2	N.	.....
215	8/22/50	2.13	...	8,150	6.29	12.6	41	0.4	N.	.....
231	9/ 7/50	2.35	...	8,700	6.15	13.2	42	1.1	N.	Vigorous, ate well, feces normal
267	10/13/50	2.67	...	16,400	5.85	13.8	44	0.9	N.	.....
319	12/ 4/50	3.06	...	15,250	5.74	13.2	43	0.2	N.	Thriving
495	2/20/51	3.42	...	14,500	6.43	12.6	44	0.2	N.	.....

Summary: A single dose of ascorbic acid during course of the experiment delayed advent of megaloblastosis. Ascorbic acid alone effected complete cure of megaloblastic marrow, anemia, diarrhea, and all other symptoms.

Monkey No. 36A, B, rhesus, male, wt. 1.65 Kg.

A: control; Diet No. 8 with ascorbic acid; B: Diet No. 8 supplemented with vitamin B_{12} and ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
50	1/19/50 to 3/10/50	1.65	... 310	13,400	4.54	9.1	35 ..	0.9 ...	N. ...	Preliminary period on milk diets with ascorbic acid
Period A										
51	3/11/50	....	...	.....	....	....	..	...	...	Diet No. 8 started
69	3/29/50	1.90	450	11,550	5.16	11.8	38	2.2	N.	.....
116	5/15/50	1.87	300	14,050	....	10.8	32	4.9	N.	.....
151	6/19/50	1.99	420	5,150 (50)	5.67	11.1	34	4.8	N.	.....
188	7/26/50	2.11	395	20,700	4.48	11.0	31	6.1	N.	.....
215	8/22/50	2.13	...	11,450	5.20	10.6	38	5.7	N.	.....
222	8/29/50	....	...	.....	....	....	..	...	...	Right lobe liver removed surgically for tissue analyses; tolerated well
Period B										
0	9/ 3/50	....	...	.....	....	....	..	...	...	Vitamin B_{12} 15 γ I.M. weekly started
3	9/ 6/50	2.00	...	14,500	3.87	9.3	33	7.9	N.	.....
18	9/21/50	2.24	...	16,000	....	9.9	..	1.5	...	.....
30	10/ 3/50	2.50	...	12,000	4.70	10.7	39	1.5	N.	.....
87	11/29/50	2.91	...	21,450	5.28	10.8	39	4.0	N.	.....
148	1/29/51	3.00	...	21,700	5.55	11.1	42	0.8	N.	.....

Summary: The animal always ate well and never had any diarrhea. There was no anemia or megaloblastosis without supplementary vitamin B_{12} but the animal gained much better after B_{12} was added. Gums bled frequently throughout both periods for unknown reason. This accounts for increased reticulocytes. The blood was well maintained in the face of small chronic blood loss. There was a fall in hemoglobin at the start of period B owing to blood loss from surgically taken biopsy.

Monkey No. 37, rhesus, female, wt. 1.76 Kg.

Vitamin B_{12} and P. G. A. given prophylactically; Diet No. 4B; no ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
52	1/19/50 to 8/12/50	1.76 2.08	... 430	12,950	6.13	13.6	49 ..	0.8 ...	N. ...	Preliminary period on milk diets with ascorbic acid
53	3/13/50	....	...	.....	....	....	..	...	...	Ascorbic acid discontinued; Diet 4B since 3/7/50
63	3/23/50	2.12	410	10,200	6.08	14.4	45	1.1	N.	15 γ B_{12} + 500 γ P.G.A. I.M. weekly
109	5/ 8/50	2.19	450	10,550	6.39	14.5	..	1.8	N.	.....
124	5/23/50	2.03	295	.....	....	....	..	...	...	Scurvy; no diarrhea
130	5/29/50	1.85	210	7,000 (100)	7.04	13.6	43	2.5	N.	Diarrhea; aureomycin 250 mg. 3 days
137	6/ 5/50	1.76	350	.....	....	10.4	..	...	N.	Scurvy severe; diarrhea since 5/28/50
144	6/12/50	1.65	340	7,400	3.73	8.3	30	20.1	N.	Diarrhea continued; very weak
148	6/16/50	....	...	.....	....	....	..	...	...	Killed for tissue analyses

Summary: Vitamin B_{12} plus P.G.A. did not prevent anemia, and marrow remained normoblastic. Aureomycin had no effect on diarrhea.

Monkey No. 39, rhesus, female, wt. 1.60 Kg.

P. G. A. given prophylactically, 500 γ orally weekly; Diet No. 4B; no ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
24	2/16/50 to 3/12/50	1.60	...	.....	....	....	..	...	...	Preliminary period on milk diets with ascorbic acid
25	3/13/50	2.06	290	13,800	5.20	12.7	40	0.6	N.	Ascorbic acid discontinued; on Diet No. 4B since 3/7/50
30	3/18/50	....	...	.....	....	....	..	...	...	500 γ P.G.A. orally weekly started
60	4/17/50	1.88	370	12,050	5.39	13.5	41	1.9	N.	No diarrhea
90	5/17/50	1.76	320	16,200	5.48	12.6	40	1.7	N.	Scurvy, periorbital hemorrhage; no diarrhea
118	6/14/50	1.57	210	13,350 (150)	4.03	8.9	30	3.6	N.	Scurvy severe for 28 days; mild diarrhea
120	6/16/50	....	...	.....	....	....	..	...	...	Killed for tissue analyses

Summary: Even oral P.G.A. in small amount prevented megaloblastosis in spite of severe prolonged scurvy. There was mild diarrhea; no antibiotics were used.

Monkey No. 40B, rhesus, male, wt. 2.40 Kg.
Folinic acid given prophylactically; Diet No. 4B; no ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	6/ 7/50	2.40	...	.....	....	....	..	...	...	Diet No. 4B started; beginning of Period B.§
33	7/10/50	2.46	345	9,150	6.45	12.8	42	1.3	N.	.....
58	8/ 4/50	2.40	215	10,750	6.00	12.2	39	1.9	N.	Anorexia; no diarrhea; inactive
59	8/ 5/50	....	...	.....	....	....	..	...	...	Folinic acid 150 γ I.M. daily 8/4/50 to 8/11/50
60	8/ 6/50	....	...	.....	....	....	..	...	...	.....
61	8/ 7/50	....	155	12,450	....	....	..	3.0	N.	Diarrhea; appetite improved
62	8/ 8/50	....	...	9,200	....	....	..	2.7	...	.....
63	8/ 9/50	2.19	...	9,750 (100)	....	....	..	3.5	...	.....
64	8/10/50	....	...	8,650	....	....	..	3.1	...	Feces formed; ate normally
65	8/11/50	....	...	7,600	....	....	..	1.3	N.	.....
76	8/22/50	2.27	425	11,500	5.80	15.0	41	0.3	N.	Ate well; no diarrhea
91	9/ 6/50	2.38	350	12,750	6.19	13.7	43	1.1	...	.....
101	9/16/50	....	...	.....	....	....	..	...	N.	Scurvy, periorbital hemorrhage; mild diarrhea
104	9/19/50	....	...	.....	....	....	..	...	N.	Folinic acid 200 γ I.M.
105	9/20/50	2.30	195	.....	....	....	..	...	...	Folinic acid 600 γ I.M.
106	9/21/50	....	...	.....	....	....	..	...	N.	Folinic acid 600 γ I.M.
107	9/22/50	....	...	.....	....	....	..	...	...	Folinic acid 600 γ I.M.
108	9/23/50	....	...	.....	....	....	..	...	...	Folinic acid 600 γ I.M.
109	9/24/50	....	...	.....	....	....	..	...	...	Folinic acid 600 γ I.M.
113	9/28/50	2.33	430	.....	....	....	..	...	...	Ate well; no diarrhea
118	10/ 3/50	....	...	4,150	5.47	12.9	42	0.3	N.	.....
138	10/23/50	2.43	280	6,850	5.49	12.3	42	0.5	N.	Scurvy severe; anorexia
148	11/ 2/50	2.17	40	9,800	5.08	9.6	..	1.2	N.	.....
155	11/ 9/50	1.67	35	7,900	3.92	8.7	29	2.0	N.	Bloody (scurvy?) diarrhea
158	11/12/50	....	...	.....	....	....	..	...	N.	Died

Summary: Folinic acid given apparently prevented megaloblastosis. Scurvy was severe and prolonged. General condition, weight, appetite, and diarrhea were also favorably influenced, even before clinical scurvy or anemia. Anemia developed terminally with severe scurvy though marrow remained normoblastic.

Monkey No. 41, rhesus, female, wt. 2.22 Kg.
Diet No. 8; no ascorbic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	2/16/50 to	2.22	...	.....	....	....	..	...	...	Preliminary period on milk diet
22	3/10/50	2.35	215	12,050	6.33	12.3	41	0.6	N.	with ascorbic acid
23	3/11/50	....	...	.....	....	....	..	...	...	Diet No. 8 started; ascorbic acid discontinued
67	4/24/50	2.40	450	11,950	6.16	13.7	41	1.3	N.	.....
95	5/22/50	2.37	460	16,200	7.25	14.5	43	1.2	N.	.....
111	6/ 7/50	2.40	450	13,550 (50)	6.54	14.4	44	0.7	N.	.....
130	6/26/50	2.38	330	21,850	7.18	13.7	42	0.4	N.	Anorexia began
140	7/ 6/50	2.11	220	.....	....	....	..	...	...	Scurvy, periorbital hemorrhage
153	7/19/50	2.07	215	8,000	4.70	8.4	28	4.3	M.	.....
160	7/26/50	1.90	240	11,350 (100)	2.99	5.8	21	7.9	M.	.....
161	7/27/50	....	...	.....	....	....	..	...	...	Killed for tissue analyses

Summary: There was never any diarrhea. The animal had the same course as milk-fed animals.

Monkey No. 45, rhesus, wt. 2.26 Kg.
Diet No. 4B; no ascorbic acid; treatment of megaloblastosis with 750 γ P. G. A. and vitamin B_{12}

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	3/ 9/50	2.26	...	.....	....	....	..	...	...	Diet No. 4B started
5	3/14/50	....	...	.....	....	....	..	...	...	Ascorbic acid discontinued
7	3/16/50	....	415	12,150	6.04	12.4	39	0.5	N.	.....
46	4/24/50	2.42	...	10,250	6.11	13.8	43	0.8	N.	.....
74	5/22/50	2.39	...	16,400	7.04	13.5	40	1.4	N.	.....
89	6/ 6/50	2.54	...	6,200	4.21	10.7	33	3.5	N.	Scurvy
95	6/12/50	2.14	260	7,350	4.67	10.4	37	6.2	N.	.....
102	6/19/50	1.83	270	12,450 (900)	3.71	8.1	25	14.0	...	Diarrhea for time
109	6/26/50	1.77	235	11,750 (1,400)	2.05	5.0	12	25.0	M.	750 γ P.G.A. + 15 γ vitamin B_{12} I.M. daily
110	6/27/50	....	...	.....	....	....	..	...	...	Same treatment
111	6/28/50	....	270	.....	....	....	..	...	...	Same treatment
112	6/29/50	....	...	.....	....	....	..	...	N.	Same treatment
113	6/30/50	....	...	.....	....	....	..	...	...	Same treatment
114	7/ 1/50	....	...	5,400 (12,300)	2.32	4.3	12	50.0	...	Died; no clinical improvement

Summary: Diarrhea did not precede megaloblastosis. There was no antibiotic treatment. The dose of P.G.A. administered was not adequate. Adequate vitamin B_{12} was given for any contribution it could make, and it apparently made none.

Monkey No. 47, rhesus, female, wt. 2.03 Kg.
Diet No. 4B; no ascorbic acid; killed for tissue analyses

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	4/18/50	2.03	...	.....	....	....	..	...	...	Diet No. 4B started
2	4/20/50	....	...	.....	....	....	..	...	...	Ascorbic acid discontinued
22	5/10/50	2.27	...	13,750	5.93	12.9	42	0.6	N.	.....
69	6/26/50	2.07	265	17,100	5.95	12.4	29	0.4	N.	.....
72	6/29/50	....	...	.....	....	....	..	...	...	Scurvy, periorbital hemorrhage
83	7/10/50	1.82	230	7,600 (200)	5.11	8.9	28	7.0	N.	.....
90	7/17/50	1.74	200	6,650 (200)	2.97	5.8	22	20.2	...	.....
92	7/19/50	....	275	21,000 (1,400)	....	5.3	20	25.0	M.	Killed for tissue analyses

Summary: Straightforward development of scurvy and megaloblastosis. There was never any diarrhea.

Monkey No. 48, rhesus, male, wt. 2.22 Kg.
Diet No. 4B; no ascorbic acid; killed for tissue analyses

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	4/18/50	2.22	...	.....	....	....	..	...	...	Diet No. 4B started
2	4/20/50	....	...	.....	....	....	..	...	...	Ascorbic acid discontinued
22	5/10/50	2.45	...	12,900	6.90	13.2	42	1.4	N.	.....
72	6/29/50	2.31	180	.....	....	....	..	...	N.	Scurvy, periorbital hemorrhage
78	7/ 5/50	2.12	140	13,800	5.18	9.8	32	2.4	N.	.....
92	7/19/50	1.62	180	6,800 (150)	3.82	8.3	27	5.4	M.	Killed for tissue analyses

Summary: There was never any diarrhea. Straightforward development of scurvy and megaloblastosis.

Monkey No. 49, rhesus, male, wt. 2.35 Kg.
Diet No. 4B; no ascorbic acid; killed for tissue analyses

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	4/18/50	2.35	...	.....	....	....	..	...	...	Started on Diet No. 4B
1	4/19/50	....	...	.....	....	....	..	...	...	Ascorbic acid discontinued
22	5/10/50	2.22	...	7,400	6.32	12.8	37	0.7	N.	.....
69	6/26/50	2.14	440	11,900	....	13.6	43	...	N.	.....
78	7/ 5/50	2.15	375	6,350 (200)	6.03	12.3	38	1.1	N.	.....
84	7/11/50	2.16	305	.....	....	....	..	...	...	Scurvy
92	7/24/50	1.95	190	3,250 (500)	3.89	8.6	28	2.2	...	.....
99	7/26/50	1.87	...	5,500 (100)	2.99	6.7	23	3.2	M.	Killed for tissue analyses

Summary: There was never any diarrhea. Straightforward development of scurvy and megaloblastosis.

Monkey No. 50, rhesus, male, wt. 1.67 Kg.
Diet No. 4B; no ascorbic acid; treatment of megaloblastosis with folinic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leukocytes	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Hematocrit	Reticulocytes per 100 RBC.	Marrow	Comments
0	4/17/50	1.67	...	.....	....	....	..	...	...	Diet No. 4B started
2	4/19/50	....	...	.....	....	....	..	...	...	Ascorbic acid discontinued
23	5/10/50	1.78	440	9,200	5.97	12.7	41	0.4	N.	.....
53	6/ 9/50 to	....	...	.....	....	....	..	...	...	Anorexia and diarrhea
62	6/18/50	1.77	150	.....	....	....	..	...	...	Gavage; aureomycin treatment
63	6/19/50	1.80	380	.....	....	12.3	..	...	M.	Ate well again
70	6/26/50	1.78	...	4,150 (250)	3.98	9.4	23	1.2	M.	Diarrhea unimproved
71	6/27/50	....	...	.....	....	8.6	26	...	...	7.5 γ folinic acid ‖ I.M. daily
72	6/28/50	....	285	6,150 (700)	3.13	7.4	24	2.1	...	.....
74	6/30/50	....	...	.....	....	....	..	...	...	Scurvy, periorbital hemorrhage
75	7/ 1/50	....	...	6,300 (400)	3.57	8.1	..	20.5	N.	.....
76	7/ 2/50	....	...	7,100 (800)	....	8.6	22	20.0	...	.....
77	7/ 3/50	1.78	450	.....	....	....	..	11.0	...	Diarrhea ceased; ate well
79	7/ 5/50	....	...	7,900	3.93	9.1	30	10.2	...	.....
82	7/ 8/50	....	450	.....	....	9.7	..	9.7	...	.....
86	7/12/50	1.77	...	.....	....	10.3	..	11.9	...	.....
88	7/14/50	....	450	.....	....	10.3	..	5.8	N.	37.5 γ folinic acid I.M. (last dose)
91	7/17/50	1.69	195	16,450	4.65	9.5	33	4.6	...	.....
96	7/22/50	....	...	5,150	3.78	8.2	..	2.7	M.	Died

Summary: The diarrhea was unaffected by aureomycin and ceased after folinic acid treatment. The effect of therapy on symptoms and megaloblastic marrow was as prompt and complete as has been obtained with much larger doses of folic acid (compare No. 24 and 45). Death was apparently due to ascorbic acid deficiency. The effect of folinic acid on marrow was unsustained, as the marrow tended to revert to the megaloblastic type eight days after therapy was discontinued.

Monkey No. 51, rhesus, male, wt. 1.74 Kg.
Diet No. 4B; no ascorbic acid; treatment of megaloblastosis with folinic acid

Day	Date	Wt., Kg.	Intake, Cc.	Leuko-cytes	Erythro-cytes, Millions	Hemo-globin, Gm./ 100 Cc.	Hema-tocrit	Reticu-locytes per 100 RBC.	Marrow	Comments
0	5/18/50	1.74	...	.....	....	....	..	...	...	Started on Diet No. 4B
4	5/22/50	1.74	...	.....	....	....	..	...	...	Ascorbic acid discontinued
6	5/24/50	....	95	10,300	5.92	11.2	38	0.6	N.	Ate poorly, diarrhea few days
38	6/26/50	1.78	450	.....	....	....	..	...	N.	Ate and gained normally
62	7/19/50	1.97	375	12,400	6.30	14.3	43	1.4	N.	.....
76	8/ 2/50	1.82	245	8,500	4.57	12.5	39	5.4	...	Scurvy, periorbital hemorrhages
96	8/22/50	1.42	140	8,350 (150)	2.26	5.6	20	14.0	M.	No diarrhea; very weak
97	8/23/50	....	...	.....	....	....	..	18.6	...	30 γ folinic acid ‖ I.M. daily
98	8/24/50	....	...	.....	....	....	..	19.0	...	.....
99	8/25/50	....	...	8,350 (4,150)	....	....	..	35.7	...	.....
100	8/26/50	....	...	9,650 (1,900)	....	....	..	25.0	N.	Stronger; ate better
102	8/28/50	....	200	8,250 (1,350)	3.50	6.0	23	20.3	...	.....
107	9/ 2/50	....	...	9,300 (100)	4.00	6.5	26	14.0	...	.....
109	9/ 4/50	1.10	185	.....	....	....	..	25.0	...	300 γ folinic acid I.M. daily
110	9/ 5/50	....	...	.....	....	....	..	18.0	...	.....
111	9/ 6/50	....	185	.....	....	....	..	20.0	...	.....
112	9/ 7/50	....	...	4,250 (150)	3.84	6.6	29	18.0	N.	Died of scurvy

Summary: Megaloblastic marrow was converted to normoblastic with smaller dose of folinic acid than folic acid (compare No. 32).

* N. stands for normoblastic.
† P.G.A. stands for pteroylglutamic acid.
‡ M. stands for megaloblastic.
§ During Period A the animal was fed Diet No. 2 (previous report [13]) with ascorbic acid for 111 days. The course was uneventful and marrow remained normoblastic.
‖ Synthetic folinic acid was prepared and supplied by the research laboratories of Eli Lilly & Company, courtesy of Dr. Edward Campbell.

ACUTE ERYTHROBLASTOPENIA IN SICKLE-CELL ANEMIA AND INFECTIOUS MONONUCLEOSIS

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AN ACUTE transitory cessation of red-blood-cell production in hereditary spherocytosis was reported by Owren,[1] who applied the term "aplastic crisis" to the precipitous drop in red-blood-cell count and hemoglobin levels noted in his patients. Similar observations have also been made by Dameshek and Bloom,[2] Horne and co-workers,[3] and others [4] on persons with familial hemolytic jaundice. Dameshek and Bloom [2] suggested that the aplastic crisis was secondary to increased splenic activity, which produced a maturation arrest of the red-cell apparatus at the pronormoblast level. Recently, Singer and associates [5] described the development of an aplastic crisis in a patient with sickle-cell anemia. The pathophysiologic mechanisms responsible for the development of such an event in the hemolytic syndromes have been extensively discussed by both Owren [1] and Singer and others.[5] No evidence of hypersplenism, either in inhibiting the marrow or in causing increased hemolysis of the red cells, was felt to be present. In sickle-cell anemia, in which an autosplenectomy [6] is not an infrequent occurrence, hypersplenism could hardly be an important factor in the development of the aplastic crisis.

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1. Owren, P. A.: Congenital Hemolytic Jaundice: Pathogenesis of the "Hemolytic Crisis," Blood **3**:231, 1948.

2. Dameshek, W., and Bloom, M. L.: The Events in the Hemolytic Crisis of Hereditary Spherocytosis, with Particular Reference to the Reticulocytopenia, Pancytopenia and an Abnormal Splenic Mechanism, Blood **3**:1381, 1948.

3. Horne, J. L.; Lederer, H.; Kirkpatrick, H. J. R., and Leep, D. G.: Familial Crises in Congenital Hemolytic Disease, Lancet **2**:33, 1945.

4. Marson, F. G.; Meynell, M. J., and Tabbush, H.: Familial Crisis in Acholuric Jaundice, Brit. M. J. **2**:760, 1950.

5. Singer, K.; Motulsky, A. G., and Wile S. A.: Aplastic Crisis in Sickle Cell Anemia: A Study of Its Mechanism and Its Relationship to Other Types of Hemolytic Crisis, J. Lab. & Clin. Med. **35**:721, 1950.

6. Rich, A. R.: Splenic Lesion in Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **43**:398, 1928.

That a similar transitory cessation of erythrocyte production could occur in hematologically normal persons was first shown by Gasser,[7] who observed such marrow signs in a variety of infectious and allergic disease processes. To this phenomenon he applied the term "acute erythroblastopenia." While a similar process in patients with hemolytic anemia leads to a striking drop in the red-blood-cell count, an acute erythroblastopenia in an otherwise hematologically normal person results in only minimal lowering of the erythrocyte and hemoglobin levels.

In view of the high incidence of sickle-cell anemia in some areas in this country, it was predicted[5] that aplastic crises may be found relatively frequently in this disease, provided that the complication is kept in mind. This communication deals with our studies during the past year, in which time we have encountered four

TABLE 1.—*Marrow Studies in Cases of Aplastic Crisis: Differential Counts of Nucleated Red Blood Cells*

Case No.	Day of Marrow Examination	E:G Ratio	Cells Per 100 Nucleated Cells					Comment
			Pronormoblasts	Basophilic Normoblasts	Polychromatophilic Normoblasts	Orthochromatophilic Normoblasts	Giant Pronormoblasts	
1	1	1:26.6	3.1	0.1	0.1	0.2	...	Increased plasma cells
	6	2.1:1	1.7	7.3	58.1	5.8	...	.....
	10	1:1.2	4.1	10.0	25.0	6.9	...	.....
2	1	1:12.2	0.9	2.3	0.3	3.7	0.4	Increased plasma cells
	4	1:4.7	4.3	0.4	0.4	0.9	0.1	.....
	6	3.6:1	4.3	73.5	5.6	1.1	0.0	.....
3	1	1:3.5	2.2	10.3	7.0	2.5	...	.....
	4	1:1.5	4.3	11.4	21.5	8.6	...	.....
	26	2.1:1	1.5	20.0	44.0	2.2	...	.....
4	1	1:65.0	1.2	0.1	0.0	0.0	0.2	Increased plasma cells
	2	1:12.5	6.8	0.7	0.0	0.0	0.0	.....
	6	1:1.4	0.5	4.6	50.3	2.5	0.0	.....
	9	1:4	1.4	3.2	15.2	0.2	0.0	.....
	24	1.35:1	5.9	12.5	35.3	3.1	0.0	.....

cases of aplastic crisis in patients with sickle-cell anemia, in addition to an acute erythroblastopenia in a child with infectious mononucleosis.

CASE HISTORIES

CASE 1.—M. B., a 30-mo.-old Negro girl known to have sickle-cell anemia since the age of 18 mo., was admitted to the hospital with joint swelling, difficulty in walking, slight cough, and moderate anorexia for a five-day period. Two siblings, aged 19 and 3 mo., showed no evidence of any illness.

Physical examination revealed a temperature of 101 F. and a pulse rate of 132. The mucous membranes were extremely pale without apparent icterus. Mild generalized lymphadenopathy was present. Examination of the chest revealed no abnormality, except for a soft, blowing systolic murmur heard best over the third left rib. The liver was palpable 3 cm. below the right costal margin. The spleen was not palpable. There was only minimal swelling

7. Gasser, C.: (*a*) Akute Erythroblastopenie: 10 Fälle aplastischer Erythroblastenkrisen mit Riesenproerythroblasten bei allergisch-toxischen Zustandsbildern, Helvet. paediat. acta **4**:107, 1949; (*b*) Akute Erythroblastopenie, Schweiz. med. Wchnschr. **79**:838, 1949.

of the left wrist and knee. Neurological examination gave normal results. Roentgenograms of the chest, long bones, joints, and skull were normal.

Laboratory Data.—The urine was normal except for a 2+ reaction for acetone and a faintly positive urobilinogen reaction. The Kahn reaction was negative. The blood showed 1,250,000 red blood cells and 7,500 white blood cells per cubic millimeter. The hemoglobin concentration was 3.5 gm. per 100 ml. The differential count showed 32% segmented neutrophils, 27% nonsegmented neutrophils, 5% eosinophils, 24% lymphocytes, 5% monocytes, and 7% plasma cells. No toxic granulation of the granulocytes was observed. Moderate numbers of target cells and sickled cells were seen in the stained blood smear. No polychromatophilia was evident, and no reticulocytes were seen.

Clinical Course.—In view of the complete absence of reticulocytes in a patient with severe sickle-cell anemia, the possibility of an aplastic crisis was immediately considered. The marrow was cellular but showed a striking absence of cells of the erythrocytic series. A moderate increase in the number of plasma cells was also noted (Table 1, Case 1). The patient was transfused with 350 ml. of whole blood. The clinical course, as reflected in both peripheral counts and marrow differential counts, is presented in Figure 1 and Table 1. During the first five days of hospitalization no evidence of red-cell delivery was apparent; after this a slowly progressive reticulocytosis developed, the count reaching a maximum of 12% by the 12th day. The marrow, which on admission had an erythrocytic-granulocytic (E:G) ratio of 1:26.6,[8] showed evidence of marked erythroid hyperplasia on the sixth hospital day, when the E:G ratio was 2.1:1.

Extensive bacteriologic and serologic studies [9] were carried out in an attempt to define the etiological agent. Blood and nose and throat cultures repeatedly yielded no pathogenic organisms. Bacterial agglutinations were negative for typhoid, tularemia, and Brucella organisms. The Weil-Felix reaction was negative. Viral and rickettsial complements-fixation tests failed to reveal organisms of the following groups: Japanese B encephalitis, Eastern and Western equine encephalitis, lymphocytic choriomeningitis, mumps, psittacosis-pneumonitis group, influenza A, A′ and B, Q fever, rickettsialpox, and epidemic and murine typhus. The heterophile-antibody titer and agglutination reaction for Streptococcus MG were negative, and there were no cold agglutinins.

Case 2.—G. N., a 5-yr.-old Negro girl with known sickle-cell anemia since the age of 6 mo., entered the Sarah Morris Hospital with complaints of listlessness, anorexia, and temperature of 102 F., for two weeks. Vomiting had occurred for three days prior to entry. She had had frequent infections of the upper respiratory tract and several admissions to this hospital for migratory joint pains and abdominal discomfort. A twin sister with sickle-cell anemia, who also complained of mild fever during the course of the patient's present illness, did not exhibit any alterations in her hematological values.

Physical examination revealed a temperature of 102.8 F. and a pulse rate of 120. No visible icterus was present. There was mild, generalized, nontender lymphadenopathy. The tonsils were moderately enlarged without being acutely inflamed. The lungs were clear. The heart was slightly enlarged to the left, with a harsh systolic murmur over the entire precordium. The liver and spleen were not palpable. The musculoskeletal system was normal. Neurological examination gave normal results.

Roentgenographic examination of the chest revealed only a minimal increase in the bronchovascular markings in the right lower lung fields. The heart was enlarged in the region of the left ventricle.

Laboratory Data.—The urine was normal except for a 3+ reaction for acetone. The blood showed 1,500,000 red blood cells, 4.33 gm. of hemoglobin, and 6,100 white blood cells, with a differential count of 35% segmented neutrophils, 22% nonsegmented neutrophils, 1% eosinophils, 26% lymphocytes, 13% monocytes, and 3% plasma cells. One nucleated red blood cell per 100 white blood cells was seen. Numerous target cells and sickled cells were present. There

8. The E:G ratio was obtained by counting 1,000 cells in unselected fields. Normal values vary from 1:2 to 1:8.

9. Dr. A. Milzer, Director of the Department of Bacteriology, Medical Research Institute, Michael Reese Hospital, performed these studies.

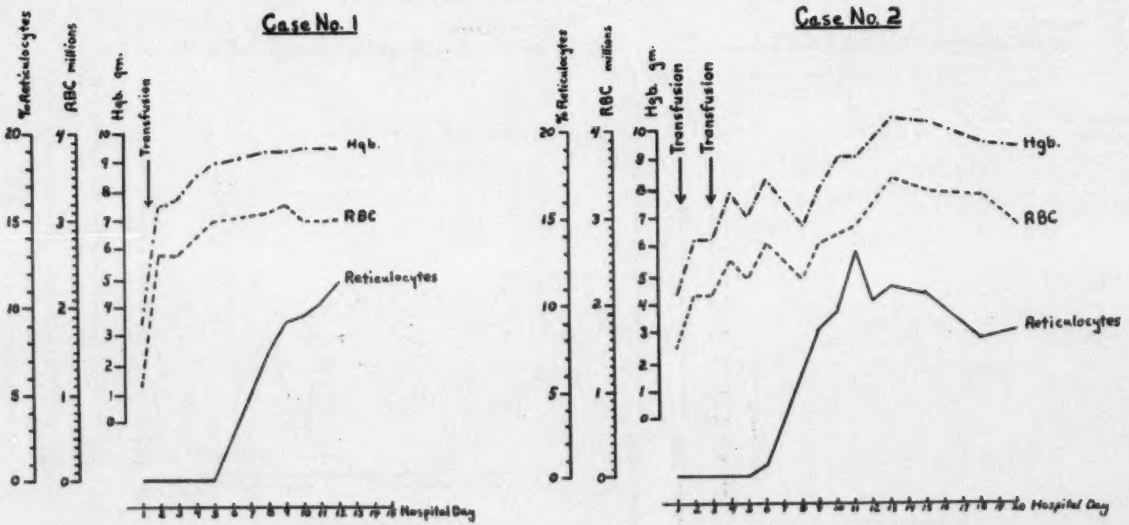

Fig. 1.—Peripheral hematologic values in aplastic crisis (Cases 1 and 2).

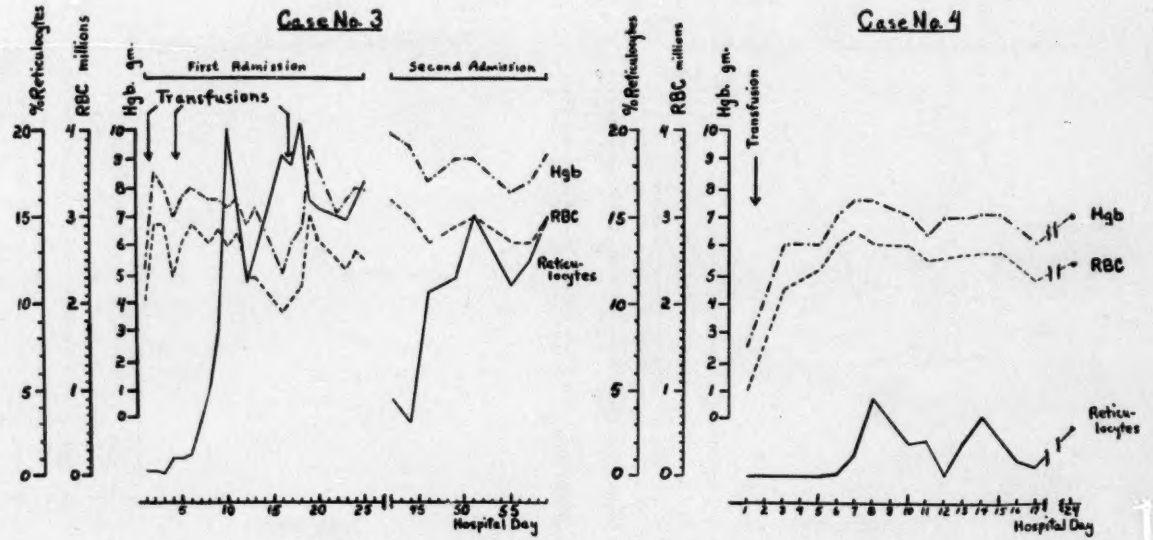

Fig. 2.—Peripheral hematologic values in aplastic crisis (Cases 3 and 4).

was no polychromatophilia on the blood smear, and no reticulocytes were seen. The Coombs reaction was negative. The marrow was cellular, but only a few pronormoblasts and orthochromatophilic normoblasts, with an occasional "giant pronormoblast," were seen (Table 1, Case 2). The E: G ratio was 1: 12.2. The granulocytic series showed a shift to the left, with a slight increase in eosinophils and a moderate increase in plasma and reticulum cells.

Course.—The diagnosis of an aplastic cirsis was, again, immediately suggested by the absence of polychromatophilia in a patient with severe sickle-cell anemia. The patient was treated with antibiotics and transfused with 300 ml. of whole blood. Extensive bacteriologic and serologic studies, similar to those carried out in Case 1, gave negative results, except for the presence of Escherichia coli in the urine on one occasion. Cold agglutinins were absent. The patient became afebrile and asymptomatic on the fourth hospital day. The hematological course is summarized in Table 1 and Figure 1, Case 2. On the fourth hospital day there occurred an increase of pronormoblasts and basophilic normoblasts in the marrow, and on the sixth day a marked erythrocytic hyperplasia developed (E: G ratio, 3.6: 1). Reticulocytosis became evident on the sixth day, and the count reached a maximum of 13% on the 11th day. Although the patient has had numerous upper respiratory infections since discharge, she has not had a second aplastic crisis.

CASE 3.—W. B., a 6-mo.-old Negro boy, was admitted to Sarah Morris Hospital with a history of having been well up to three days before admission, when it was noted that he felt extremely warm and had a cough and stuffy nose. One day prior to admission the patient had three generalized convulsions, each lasting three to seven minutes.

Physical examination revealed a well-developed, well-nourished infant who appeared acutely ill. The temperature was 101.8 F.; the pulse rate was 126. There was moderate pallor of the conjunctivas and buccal mucosa. No scleral icterus was evident. The anterior fontanel was somewhat full. The left tympanic membrane was injected but not bulging. Mild, nontender, generalized lymphadenopathy was present. The heart and lungs were normal. The liver was felt 3 cm. below the right costal margin. The spleen was not palpable. No neurological abnormalities were noted.

Fluoroscopy revealed marked cardiac enlargement in the region of the right ventricle and pulmonary outflow tract. Three days later, however, cardiac size was seen to be normal on roentgenogram. The lung fields were clear. A lumbar puncture, done on admission, revealed nothing abnormal.

Laboratory Data.—The urine showed a 2+ reaction for albumin, 15 to 20 hyaline casts, and 15 to 20 finely granular casts per high-power field. No hematuria was noted. The blood studies revealed 2,020,000 red blood cells, 5.3 gm. of hemoglobin, and 4,700 white blood cells, with a differential count of 1% segmented neutrophils, 63% nonsegmented neutrophils, 1% eosinophils, 28% lymphocytes, and 7% monocytes. Many target cells and sickle cells were seen in the smear. Polychromatophilia was absent, and the reticulocyte count was 0.6%. The marrow was quite cellular, with an E: G ratio of 1: 3.5. No increase in plasma cells was apparent (Table 1, Case 3).

Course.—On admission, the patient was given fluids parenterally, and treatment was started with penicillin, gantrisin® (3,4-dimethyl-5-sulfanilamido-isoxazole), and acetylsalicylic acid. After initial hematological data were obtained, the patient was transfused with 100 ml. of whole blood. Blood cultures drawn on the day of entry were reported positive for Salmonella choleraesuis. This organism proved to be most sensitive to gantrisin.® Spinal fluid, nose and throat, and stool cultures were negative for pathogenic organisms. The patient's course was one of slow improvement, complicated by two episodes of severe diarrhea. Small supportive blood transfusions were given on two occasions, as indicated in Figure 2, Case 3. Repeated blood cultures were sterile, and the patient was discharged, asymptomatic, on the 26th hospital day.

The presence of sickle cells on the peripheral blood smear obtained on admission was considered indicative of sickle-cell anemia. However, the almost complete absence of reticulocytes raised a question concerning the validity of this diagnosis. As noted above, the initial marrow findings were quantitatively within normal limits. However, the subsequent course substantiated the diagnosis of sickle-cell anemia with beginning recovery from an aplastic crisis. Repeat marrow examinations revealed a progressive increase in the numbers of red-cell precursors, with the classic picture of erythrocytic hyperplasia soon becoming established (Table 1, Case 3). It is quite possible that this patient had as severe a degree of erythroblastopenia as did each of

the first two patients, despite the fact that 0.6% reticulocytes was noted on admission. One may postulate that the period of severest erythroblastopenia occurred three to five days before the first marrow studies, with the phase of recovery becoming noticeable by the time of entry.

Seventeen days following his discharge, the patient was readmitted because of a recurrence of severe diarrhea. Stool cultures were now positive for S. choleraesuis, and treatment with terramycin was instituted. At this time, the blood picture was that of typical sickle-cell anemia, with numerous reticulocytes being present. The subsequent hematological course is presented in Figure 2, Case 3. The patient's condition improved rapidly, with complete disappearance of the pathogenic organisms from the stool. On the eighth hospital day, diarrhea reappeared and the stool cultures yielded Proteus mirabilis. Therapy with sulfonamides resulted in a rapid resolution of the disease process, and the patient was discharged on the 16th hospital day.

Agglutination tests for the Salmonella group of organisms gave negative results during the first hospital admission. However, serum drawn during his second hospitalization agglutinated the Salmonella grown from the patient's stool in a titer of 1: 320. No cold agglutinins were demonstrable, and the heterophile-antibody titer was 0.

CASE 4.—B. L., a 15-yr.-old Negro boy with known sickle-cell anemia, was admitted to Michael Reese Hospital because of convulsive movements of the upper portion of his body without loss of consciousness or incontinence. Five days prior to admission he had had a sore throat, coryza, mild nonproductive cough, and low-grade fever. These symptoms became progressively worse, with the development of shaking chills, marked fever, and dyspnea. No chest pain or hemoptysis was noted. The past history was noncontributory, except for numerous periods of hospitalization for exacerbations of his sickle-cell disease.

Physical examination revealed an underdeveloped boy who appeared acutely ill. The temperature was 103.4 F., the pulse rate, 126, and the respiration rate, 24. The blood pressure was 104/64. The mucous membranes were pale without being icteric. Moderate, generalized, tender lymphadenopathy was present. The lung fields were clear. The heart was slightly enlarged to the left. There was an apical presystolic gallop, with harsh systolic murmurs heard over the entire precordium, and a systolic thrill was felt over the apical region. The liver was palpated 2 cm. below the right costal margin. Splenomegaly could not be detected. The extremities showed no abnormalities except for a scar over the medial aspect of the right ankle, probably the site of a healed ulcer. Neurological examination revealed irritability and some clouding of the sensorium. Transient spasticity of the left arm and both lower extremities and the presence of a bilateral Babinski sign were noted.

A roentgenogram of the chest demonstrated an increased transverse diameter of the heart. There was a diffuse increase in the pulmonary vascular markings, as well as interstitial pneumonitis extending from both hilar regions into the mid-lung fields.

Laboratory Data.—The urine was normal. The Kahn reaction was negative. The blood studies showed 1,200,000 red blood cells, a hemoglobin concentration of 2.4 gm. per 100 ml., and 16,600 white blood cells, with a differential count of 61% segmented neutrophils, 8% nonsegmented neutrophils, 14% lymphocytes, and 17% monocytes. There was no polychromatophilia on the blood smear, and no reticulocytes were seen.

Course.—After admission, the patient was placed in an oxygen tent; treatment with antibiotics was instituted, and 1,000 ml. of whole blood was given. The marrow was quite cellular, but except for a few pronormoblasts, some of which were "giants," no other elements of the red-cell series were seen. Plasma cells and lymphocytes were increased in number (Table 1, Case 4). During the next 24 hr., the patient's neurological status returned to normal and his general condition improved. A repeat chest roentgenogram on the fourth hospital day showed definite resolution of the pulmonary changes. The patient continued to have a low-grade febrile course and a persistent nonproductive cough. Bacteriologic studies gave entirely negative results, except for a 1: 10 cold-agglutinin titer, which is of doubtful significance.

The hematological course of this patient is graphically represented in Figure 2, Case 4. On the second hospital day the marrow showed evidence of beginning red-cell production, but on the ninth day a reversion to a relative state of erythrocytic hypoplasia was noted (Table 1, Case 4). Not until shortly before discharge was the change to a definite erythrocytic hyperplasia obvious. The peripheral reticulocyte counts reflected this relative lack of erythrogenesis

and reached a maximum of only 4.8% on the eighth hospital day. Despite the hematological relapse as reflected in the marrow findings, no striking decrease in the red-cell count or hemoglobin levels developed. Re-examination of the patient one week after discharge revealed a marked erythrocytic hyperplasia, with an E:G ratio of 1.35:1.

Case 5.—K. M., a 4-yr.-old Negro boy, was admitted to the Sarah Morris Hospital with a history of vague pains in the extremities for 24 hr. prior to admission. The past history was essentially normal, except for a slight upper respiratory infection three weeks before entry.

Physical examination revealed a well-developed, well-nourished child who did not appear acutely ill. The temperature was 100.4 F.; the pulse rate was 98. The mucous membranes of the nose and pharynx were slightly injected. Neither icterus nor lymphadenopathy was present.

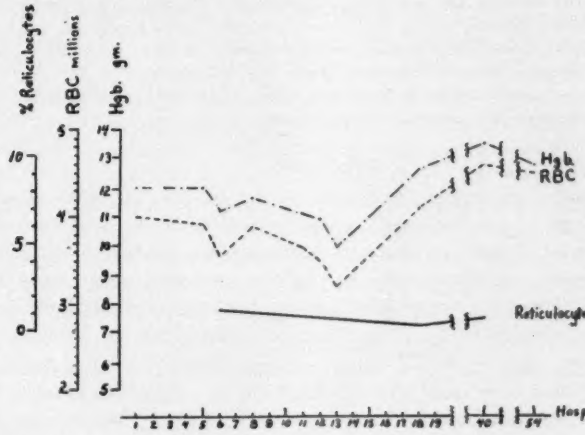

Fig. 3.—Peripheral hematologic values in patient (Case 5) with erythroblastopenia in infectious mononucleosis.

Table 2.—*Marrow Studies in Patient (Case 5) with Erythroblastopenia in Infectious Mononucleosis*

Day of Marrow Examination	% of Total Nucleated Cells			E:G Ratio	Cells per 100 Nucleated Cells			
	Granulocytic Series	Erythrocytic Series	Lymphocytes		Pronormoblasts	Basophilic Normoblasts	Polychromatophilic Normoblasts	Orthochromatophilic Normoblasts
3	44.3	5.7	50.0	1:7.8	0.2	0.4	2.5	2.6
18	35.4	20.4	44.2	1:1.7	0.7	2.6	5.8	11.3

The heart and lungs were within normal limits. The liver was palpable about 3 cm. below the right costal margin and had a smooth, nontender edge. The spleen was not palpable. Except for slight swelling and tenderness of the left ankle joint, the musculoskeletal system was without abnormality. Neurological examination gave normal results.

Laboratory Data.—Urinalysis showed no abnormality, and the Kahn reaction was negative. Blood studies showed 4,000,000 red blood cells, 12.1 gm. of hemoglobin, and 56,000 white blood cells, with a differential count of 14% segmented neutrophils, 3% nonsegmented neutrophils, 3% eosinophils, 1% basophils, 74% lymphocytes, 4% monocytes, and 1% plasma cells. Many of the lymphocytes were of the infectious-mononucleosis type, with marked variability of the nuclei. The sickle-cell test gave a negative reaction. A chest roentgenogram was within normal limits.

In view of the extremely high white-blood-cell count, marrow aspiration was performed to rule out possible leukemia. Surprisingly, a marked reduction in the numbers of red-cell precursors was observed, in addition to an increase in lymphocytes (50% of nucleated elements), many showing the characteristics of infectious-mononucleosis cells (Table 2). The positive heterophile-antibody titer of 1 : 40 (absorbed, Davidsohn technique) confirmed the diagnosis.

Course.—The patient was treated symptomatically and felt completely well by the third hospital day. There was no residual joint swelling, and the liver was no longer palpable. Hematologically, the patient presented several interesting features. The white-blood-cell count continued at very high levels for some time and did not return to normal limits for more than six weeks. Of greater interest was the slow, but definite, development of mild anemia. In view of the relative absence of red-cell precursors in the marrow, such a drop in red-cell count and hemoglobin concentration was not entirely unexpected. Unfortunately, frequent marrow examinations were not feasible, so that the period of relative erythroblastopenia could not be definitely delineated. Nevertheless, sternal aspiration carried out three weeks after admission revealed normal erythrogenesis. Concomitant with the normalization of the marrow, the erythrocyte level was noted to return toward normal. At present, the heterophile-antibody titer is 0 and the hematological picture is entirely normal.

COMMENT

1. *Etiology of Acute Erythroblastopenia.*—From the evidence in the literature [10] and from our own studies, no single, specific etiological agent can be incriminated in the pathogenesis of acute transitory erythroblastopenia. Rather, this phenomenon seems to represent a reaction on the part of the marrow to a variety of disease processes. A number of examples of aplastic crises in hereditary spherocytosis, which appeared simultaneously or in rapid succession in several members of the same family, have been reported.[11] Many of these persons showed signs of upper respiratory infection. Dedichen [11d] noted manifestations of such an infection in one person not afflicted with familial hemolytic jaundice, while a crisis occurred in the hematologically abnormal members of the same household. Horne and co-workers [3] found suggestive evidence for influenza in another such family. Gasser [7b] described a case of erythroblastopenia in a hematologically normal person with primary atypical pneumonia. This same author also noted erythroblastopenia in patients with diphtheria, allergic reactions to drugs (phenobarbital [luminal®]; chenopodium oil), after an insect bite, and in patients with anaphylactoid purpura. The patient of Singer and associates [5] had primary atypical pneumonia with a markedly elevated cold-agglutinin titer.

In the five cases reported in this communication, one occurred during the course of a S. choleraesuis septicemia, a second occurred during the course of infectious mononucleosis, and the remaining three seemed to be related to vague upper respiratory infections. In the latter group no specific causation could be proved, although extensive bacteriologic and serologic studies were carried out.

It is of interest that W. B. (Case 3) experienced a relapse of his primary disease process, yet no recurrence of the erythroblastopenic reaction took place. On the other hand, B. L. (Case 4), continuing to have a slight cough, rhinitis, and a

10. Footnotes 1 to 5 and 7.

11. (*a*) Horne and others.[3] (*b*) Marson and others.[4] (*c*) Dameshek, W.: Familial Hemolytic Crisis, New England J. Med. **224**:52, 1941. (*d*) Dedichen, H. G.: "Holla-syken": Epidemic Occurrence of Anemia Crises in Hemolytic Jaundice, Norsk. mag. laegevidensk. **98**:279, 1937.

temperature elevation, showed a hematological relapse, so far as a second period of erythroblastopenia ensued.

The frequency with which infectious and allergic processes are associated with erythroblastopenia is too great to be merely coincidental. Furthermore, the relatively high proportion of cases with probable virus causation suggests that this association may be more frequent than is generally realized. Since there is usually no indication for doing marrow aspirations in otherwise hematologically normal persons, such reactions will escape detection. Only by accumulating a much larger series of observations may the role of virus infections in the development of acute erythroblastopenia become clear.

2. *Morphologic Aspects of Marrow Alterations.*—The common denominator in almost all instances of acute erythroblastopenia is the striking disappearance of most of the red-cell precursors, with the exception of a few pronormoblasts. In some instances, large basophilic cells, with a diameter of up to 60 microns, closely resembling pronormoblasts in nuclear structure and staining characteristics, have been observed.[12] According to Undritz,[13] these "giant cells" represent the product of abnormal and incomplete mitoses of the earliest red-cell progenitors. We have noted the presence of such "giant cells" in only two of our five patients. Dameshek and Bloom [2] have interpreted the pathologic changes in the red-cell apparatus in their cases of aplastic crisis in hereditary spherocytosis as representing a maturation arrest at the pronormoblast level secondary to increased splenic activity. On the other hand, others have been unable to find an absolute increase in the numbers of the most immature red cells.[14] Differential counts done on aspirated marrow specimens during the erythroblastopenic phase in our series of cases also suggest that the absolute number of pronormoblasts is well within the range of normal (0.5 to 5%).[15]

The phase of erythroblastopenia has been noted to last as long as 10 days,[10] at which time evidence of regeneration of the red-cell apparatus becomes manifest. Within four days after the marrow shows a resumption of erythropoietic activity, release of reticulocytes may be expected. Extreme degrees of erythrocytic hyperplasia may be noted during the height of the recovery phase.[5]

Other alterations in the structure of the marrow will depend upon the type of disease with which the erythroblastopenia is associated. Thus, Gasser,[7] has observed eosinophilia in his patients with allergic backgrounds, and we and others [5] have observed significantly increased numbers of plasma cells in our patients with proved or probable virus infections. In the one instance of infectious mononucleosis, many lymphocytes, some of which were of the atypical variety, were noted. No striking changes in the other marrow constituents have been detected, although transient thrombocytopenia and leukopenia have been reported in the peripheral blood.[16]

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12. Owren.[1] Dameshek and Bloom.[2] Gasser.[7]

13. Undritz, E.: Akute Erythroblastopenie von Conrad Gasser, Schweiz. med. Wchnschr. 79:840, 1949.

14. Owren.[1] Dameshek and Bloom.[2] Gasser.[7a]

15. Leitner, S. J.: Bone Marrow Biopsy, New York, Grune & Stratton, Inc., 1949, pp. 18-19.

16. Dameshek and Bloom.[2] Singer and others.[5]

3. *Dynamic Aspects of Acute Erythroblastopenia.*—The effect which an acute cessation of red-cell production will have on the state of the organism will, in general, depend upon the presence or absence of a pre-existing hemolytic anemia. It has been well established that the survival time of the normal erythrocyte is approximately 120 days.[17] Thus, about 0.83% of the red-cell population is destroyed a day. Since, physiologically, the erythrocyte level remains relatively constant, an equivalent number of erythrocytes must enter the circulation during the same period. The actual red-cell count represents, therefore, a balance between the rates of delivery and disintegration. If delivery of erythrocytes from the marrow, for whatever reason, is interfered with, a decrease in red-cell level will manifest itself, directly related to the duration of the cessation of red-cell discharge.[5] If the rate of destruction is within the normal range and the inhibition of red-cell production of short duration (up to 10 days), a slight decrease in the red-cell count, amounting to about 1% a day, may be expected. Such a drop was observed in our case of infectious mononucleosis with erythroblastopenia in which there was a fall of the hemoglobin level from 12.1 to 9.8 gm., with a corresponding decrease of the red-cell count from 4,000,000 to 3,200,000 in 13 days. Unless specifically sought for, a decrease of this magnitude will usually be considered within the limits of error of the laboratory procedure used for the determination of these values.

If the erythroblastopenia is associated with an increased rate of erythrocyte disintegration, as exists in the hemolytic syndromes, a dramatic fall of the red-cell level is to be expected. In sickle-cell anemia the erythrocytes have been shown to survive within the circulation 15 to 60 days.[18] Since in this disorder the erythrocyte level remains relatively constant for long periods, although at a low level, a compensatory increase in red-cell delivery must be present, evidenced clinically by an erythrocytic hyperplasia of the marrow and an elevated reticulocyte count in the peripheral blood. Should an acute cessation of erythrocyte delivery take place in such a person, a precipitous drop in red-cell and hemoglobin values will soon become apparent. Singer and co-workers [5] noted approximately a 50% reduction in the red-blood-cell and hemoglobin levels by the third day of their patient's illness. Seven months later, after complete recovery, survival-time studies of the patient's erythrocytes were carried out, and, again, about 50% of the transfused red cells disappeared within a three-day period, the remainder being completely eliminated by the 28th day. Thus, it seems likely that the rapid drop in the patient's red-cell count during the first phase of his illness could be entirely explained on the basis of an absent delivery plus the rapid disintegration of extremely pathologic cells during this time interval. As Owren [1] and Singer and associates [5] have pointed out, no additional hemolytic mechanism acting to increase the rate of red-cell disintegration is necessary to explain this phenomenon.

The severity of an aplastic crisis will, therefore, depend on two main factors: first, the duration of the period of erythroblastopenia, and second, the survival time of the patient's red cells. Whereas a 10-day period of absent erythrocyte delivery

17. Callender, S. T. E.; Powell, E. O., and Witts, L. J.: The Life Span of the Red Cell in Man, J. Path. & Bact. **57**:129, 1945.

18. Singer and others.[5] Callender, S. T. E.; Nickel, J. F.; Moore, C. V., and Powell, E. O.: Sickle Cell Disease: Studied by Measuring the Survival of Transfused Red Blood Cells, J. Lab. & Clin. Med. **34**:90, 1949.

in an otherwise hematologically normal person will produce negligible effects, a process of similar duration in a patient with a hemolytic anemia, whose erythrocytes have a survival time of only 15 days, may well prove fatal. Furthermore, as has been pointed out,[18] persons with sickle-cell anemia frequently show "mixed population" curves when the lifespan of their erythrocytes is determined. In such instances, a portion of the red-cell population may be destroyed within an extremely short space of time, whereas the remainder disappears at a slower, but still pathologic, rate. The greater the proportion of erythrocytes with an extremely short lifespan, the more intense will be the reaction to an absence of red-cell delivery. In those persons with red-cell survival times of longer duration, or in whom the proportion of extremely labile erythrocytes is relatively small, the effects of an acute erythroblastopenia will be less dramatic.

Case 4 of our series provided an excellent opportunity to observe the interplay of the two mechanisms involved. As can be noted in Figure 1, Case 4, extremely low red-cell and hemoglobin values were noted on admission. The marrow showed an almost complete absence of erythrogenesis, and no new erythrocytes were entering the circulation. In a few days before hospitalization the most labile red cells had probably completed their lifespan, and the count had, therefore, dropped to a dangerously low level. After a short period of improvement, during which the patient's marrow showed signs of increased erythrocytic activity, a second period of erythroblastopenia developed. No striking decrease in the red-cell count took place, however, because (1) most of the cells with an extremely short survival time had been eliminated during the first episode of absent erythrogenesis, (2) the patient's own remaining circulating cells, although pathologic, did not disappear at a rate fast enough to repeat the dramatic crisis noted on admission, and (3) many normal red cells were also present as a result of previous blood transfusion.

4. *Diagnostic Criteria.*—In a patient with well-established hemolytic anemia the diagnosis of an acute erythroblastopenia presents little difficulty, provided the lack of polychromatophilia on the blood smear is noted.[5] A dramatic and precipitous drop in red-cell count and hemoglobin levels may be predicted and observed.[5] Often, however, the patient is first seen when his count has already reached dangerously low levels. In either instance, a definitive diagnosis is possible only on examination of the marrow, which reveals a marked diminution in the number of red-cell precursors. It should be pointed out that if the initial marrow examination is delayed for some time the aplasia may not be as profound as observed in some of the cases reported in this communication. By means of serial marrow aspirations, the return to normal marrow activity can be demonstrated,[19] and a peripheral reticulocytosis may be expected four days following the reappearance of basophilic normoblasts. This observation is in keeping with data obtained from marrow cultures which suggest that the maturation period from the pronormoblasts to the reticulocyte requires approximately four days.[20]

In the absence of a hemolytic anemia, the diagnosis of acute erythroblastopenia may present considerable difficulty. The striking clinical features of the aplastic crisis are lacking. A slowly progressive drop in red-blood-cell count and hemo-

19. Owren,[1] Singer and others.[5]

20. Fieschi, A., and Astaldi, G.: La cultura in vitro del midollo osseo, Pavia, Italy, Tipografo del Libro, 1946.

globin levels may be noticed, but such minor variations in these values are often overlooked. The only certain way of recognizing this complication depends, therefore, upon the demonstration of a diminished erythrogenesis by marrow studies. With the increasing knowledge that this reaction is apparently not infrequently associated with virus infections, examination of the marrow in such disease processes will undoubtedly uncover more instances of erythroblastopenia.

5. *Clinical Course and Treatment.*—In the person whose illness is not complicated by hemolytic anemia, no specific therapy beyond that required for the underlying disease is needed, since the period of marrow dysfunction is usually brief. In patients who have an aplastic crisis, however, vigorous therapy may be required as a lifesaving measure. As the red-cell count may drop to dangerously low levels, we have transfused all such patients immediately after the diagnosis has been made. In sickle-cell anemia, in which the patient's body functions are adapted to hemoglobin values of 7 to 8 gm. per 100 cc. and red-cell counts of about 2,500,000 per cubic millimeter, a restoration of this level is sufficient. Specific therapy for the underlying disease is carried out as in the uncomplicated cases. In the event of a more prolonged erythroblastopenic phase, further therapy with blood transfusions will depend upon careful clinical evaluation of the marrow findings. In general, the patient will have returned to his usual hematological status at the end of a two- to three-week period. Nevertheless, as Case 4 of our series demonstrated, cycles of erythroblastopenia may be encountered. In such instances recovery may be delayed for longer periods.

SUMMARY

Five cases of acute, transitory erythroblastopenia are reported. Four of these reactions occurred in patients with sickle-cell anemia leading to the development of an aplastic crisis, i. e., a precipitous and dramatic fall in red-cell count and hemoglobin levels. The fifth developed in a child with infectious mononucleosis and resulted in only minor alterations of the patient's hematological values.

Acute erythroblastopenia is interpreted as representing a reaction on the part of the marrow to a variety of noxious agents. Its occurrence during the course of a Salmonella chloeraesuis infection and in a patient with infectious mononucleosis is reported for the first time. The remaining three instances of erythroblastopenia developed in children with infections of the upper repiratory tract.

The pathophysiologic aspects of such an acute cessation of red-cell production are briefly reviewed. The marrow picture, clinical course, and therapy of this syndrome are discussed.

METHYLTESTOSTERONE TREATMENT OF PREMATURE INFANTS

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AND
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THE REPORTS on the beneficial effects of methyltestosterone for premature infants vary. Shelton and Varden [1] and Shelton, Varden, and Mark [2] found it of benefit in two series of premature infants in decreasing the expected mortality, increasing the daily weight gain, and shortening the hospital stay. Hardy and Wilkins [3] and Seitchik and Agerty [4] in their two series did not find any beneficial results over ordinary nursery treatment of premature infants. Earle,[5] using methyltestosterone and plasma orally, found them of benefit in increasing daily weight gain and in shortening the hospital stay; however he was unable to attribute his results to methyltestosterone alone, to plasma alone, or to the combination of methyltestosterone and plasma.

In an effort to evaluate further the use of methyltestosterone,[6] 50 premature infants, including four sets of twins, were studied. All premature infants were handled by a standard nursery regimen. Feedings consisted of half-skimmed milk with 10% added carbohydrate, as in the regimen used by Hardy and Wilkins.[3] This formula supplied 120 to 130 Cal. per kilogram daily.

Alternate premature infants were included with no regard for sex or race. Those who expired before the 10th day of life or during the test period were not included in the study as we were concerned mainly with increase in weight and length of hospital stay and not with the fatality rate. Premature infants weighed less than 2,000 gm.; the birth weights in the study group ranged from 794 gm. to 1,928 gm. and averaged 1,600 gm. In the control group the birth weights ranged from 1,447 to 1,928 gm. and averaged 1,702 gm. Five milligrams of methyltestosterone in propylene glycol in 20% alcohol was given orally once daily, starting between the fourth and 18th day (average, 10th day), and was continued for 14 to 36 days with an average of 24 days. The average starting day (the 10th) allowed for the natural tendency of the weight of most premature infants to reach a plateau or start to increase.

From the Department of Pediatrics, University of Arkansas School of Medicine; Journal Series No. 959.

1. Shelton, E. K., and Varden, A. E.: The Use of Methyl Testosterone in the Treatment of Premature Infants, J. Clin. Endocrinol. **6:** 812, 1946.

2. Shelton, E. K.; Varden, A. E., and Mark, J. S.: Experimental Use of Testosterone Compounds in Premature Infants, J. Clin. Endocrinol. **7:** 708, 1947.

3. Hardy, J., and Wilkins, L.: Methyl Testosterone in the Treatment of Premature Infants, J. Pediat. **34:** 439, 1949.

4. Seitchick, J. N., and Agerty, H. A.: Experimental Use of Methyl Testosterone in Premature Infants, Pediatrics **5:** 200, 1950.

5. Earle, A. M.: Methyl Testosterone and Plasma for Premature Infants, J. Pediat. **36:** 87, 1950.

6. Methyltestosterone was supplied gratuitously by Edward Henderson, M.D., of the Schering Corporation, of Bloomfield, N. J.

COMMENT

There was no significant difference in weight gain between the control group and the treated group. (By Fisher's t test, P is approximately 0.056.) The treated group averaged 2.1 gm. more in their daily weight gain while being treated than the control group, and in 19 treated and 19 control infants matched as to sex, color, and approximate birth weight there was an average daily weight gain of 3.4 gm. more for the treated than for the control infants. The treated group averaged 2.4 gm. more for their daily average weight gain from birth to discharge than the control group.

The table shows that the treated group was in the hospital 8.5 days longer than the control group; however two treated infants were in the hospital 77 and 78 days. If these are excluded, the hospital stay for the other 23 averaged 36.2 days, and for the 25 controls the duration was 32.7 days. We did not regard this difference as significant, since the treated infants weighed on the average of 100.2 gm. less than the controls.

Premature Infants Treated with Testosterone and Control Group

	Groups	
	Treated	Control
Number of patients	25	25
Negro males	4	8
Negro females	9	10
White males	3	3
White females	9	4
Average birth weight—gm.	1,600	1,702
Average day testosterone started	10th	..
Average no. of days on testosterone	24	..
Average no. of days to regain birth wt.	13.8	12.1
Average daily gain while on testosterone or control period—gm.	32.9	30.8
19 prematures matched as to sex and approximate birth weights. Average daily gain—gm.	31.2	27.8
Average daily gain from birth to discharge—gm.	21.9	19.5
Average total days in hospital	41.2	32.7
Average discharge weight—gm.	2,485	2,404

Only one treated patient showed an untoward effect from the methyltestosterone that could be detected clinically. This consisted of definite enlargement of the clitoris in a premature infant that weighed 794 gm. at birth. In the instances of the twins, the twin weighing less was treated with methyltestosterone and the heavier twin used as a control; there was no significant difference in weight gain or length of hospital stay.

SUMMARY

Fifty premature infants including four sets of twins were studied, 25 in the control group and 25 in the treated group.

There was no significant difference in the weight gains of either group.

The duration of hospitalization was not markedly shortened in the treated group.

Methyltestosterone alone in daily doses of 5 mg. was of no significant benefit in increasing the weight gain of premature infants.

NEUROBLASTOMA

Review of the Literature and Report of Six-Year Cure by Roentgen Therapy

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AND
PHILIP J. HOWARD, M.D.
DETROIT

A REVIEW of the subject of neuroblastoma seems justified because of the change in prognosis associated with this tumor. Our case, in which the patient seems well at the age of 6 yr., illustrates androgen increase, shown by well-developed acne at the age of 9 weeks. Androgenic material is not secreted by the tumor tissue itself and must be understood as resulting from a mechanical stimulation of the nearby adrenal cortex. Most authors in the past found a very poor prognosis after a diagnosis of neuroblastoma was made. Blacklock [1] felt that the average duration of life was eight to nine weeks. Doub [2] reported three patients in 1937 who lived an average of four and one-third months after the diagnosis was made. Even more recently, Judge,[3] in 1949, reported the prognosis to be hopeless. Lewis and Geschickter [4] in 40 cases found the average life span after diagnosis to be only six months, and Redman [5] found the duration of symptoms to be two to five months in his series; yet there are increasing numbers of cures reported in the literature. Lehman [6] in 1932 reported a patient alive 15 yr. after diagnosis. Roussy [7] reported a patient with metastases alive several years after treatment. Wyatt and Farber [8] in 1941 reported 40 cases. Ten of the patients were alive two to five years after the diagnosis. In 1950 Wittenborg [9] described treatment in 73 of the 143 cases of neuroblastoma recorded at the Children's

From the Department of Pediatrics, Henry Ford Hospital.

1. Blacklock, J. W. S.: Neurogenic Tumors of the Sympathetic System in Children, J. Path. & Bact. **39**:27, 1934.

2. Doub, H. P.: The Roentgen Aspect of Sympathetic Neuroblastoma, J. A. M. A. **109**:1188 (Oct. 9) 1937.

3. Judge, D. J.; Olshaker, B.; Kaufman, P.; Kuder, H., and Vaden, E.: Neuroblastoma, Clin. Proc. Child. Hosp. **5**:115, 1949.

4. Lewis, D., and Geschickter, C. F.: Tumors of Sympathetic Nervous System: Neuroblastoma, Paraganglioma, Ganglioneuroma, Arch. Surg. **28**:16 (Jan.) 1934.

5. Redman, J. L.; Agerty, H. A.; Barthmaier, O. F., and Fisher, H. R.: Adrenal Neuroblastoma: Report of Case and Review of Literature, Am. J. Dis. Child. **56**:1097 (Nov.) 1938.

6. Lehman, E. P.: Adrenal Neuroblastoma in Infancy—15 Year Survival, Ann. Surg. **95**:473, 1932.

7. Roussy, G.; Huguenin, R.; Perrot, M., and Saracino, R.: Evolution d'un cas de sympathome embryonnaire, Rev. neurol. **73**:32, 1941.

8. Wyatt, G. M., and Farber, S.: Neuroblastoma Sympatheticum: Roentgenological Appearances and Radiation Treatment, Am. J. Roentgenol. **46**:485, 1941.

9. Wittenborg, M. H.: Roentgen Therapy in Neuroblastoma, Radiology **54**:679, 1950.

Medical Center of Boston; 22 of the 73 patients treated were doing well three or more years after receiving therapy. With this mounting evidence of some recovery from neuroblastoma, the hopeless prognosis must be moderated, and the importance of early diagnosis and treatment becomes of much more value.

In 1947 Mandeville [10] found 431 cases reported in the literature to that time. Since then we find that Beneventi and Twinem [11] reported 10 patients who were well three to eight years after discovery of the tumor. Van Creveld and van Dam [12] reported one patient alive five years after treatment. Judge [3] reported three cases; Steiner [13] discussed 16 cases; Murray and Stout [14] reported eight cases, in one of which the patient was well after 18 mo., and Bergan [15] reported one case. Other cases have been reported by Cox,[16] Ryder,[17] Larimer,[18] and the St. Louis Children's Hospital.[19] Including our own case, the total number of reported cases of neuroblastoma is 475. Included in this figure are 47 cases reported as cures, or about 10% of the total number. There must be many other cases that have not been reported, as well as those cases that were described as sarcomas in the early literature.

HISTORY AND PATHOLOGY

Before 1863 all tumors that are now termed neuroblastoma, sympathicoblastoma, sympathoblastoma, neuroblastoma sympathicum, or neurocytoma were classified as round-cell sarcomas of the adrenal gland or lymphosarcomas. It was at this time that Virchow [20] recognized this tumor, but he referred to it as a glioma. In 1885 Dalton [21] reported a typical case of neuroblastoma of the adrenal gland with metastases to the liver, which he classified as lymphosarcoma. In 1891 Marchand [22] noted the resemblance of this tumor to that of the developing central nervous system. Pepper [23] in 1901 partly recognized this tumor when he described a case of a 6-week-old infant with tumor involvement of the liver and right

10. Mandeville, F. B.: Sympathoblastoma (Neuroblastoma), Adrenal, Abdominal, and Mediastinal, Urol. & Cutan. Rev. **51**:448, 1947.

11. Beneventi, F. A., and Twinem, F. P.: Neuroblastoma, J. Urol. **60**:235, 1948.

12. van Creveld, S., and van Dam, R.: Prognosis in Sympathoblastoma, Acta pædiat. **34**:279, 1947.

13. Steiner, P. E.: Case Reports of Children's Memorial Hospital **6**:883, 1947.

14. Murray, M. R., and Stout, A. P.: Distinctive Characteristic of the Sympathicoblastoma Cultivated in Vitro: Method for Prompt Diagnosis, Am. J. Path **23**:429, 1947.

15. Bergan, F.: Maligne retroperitoneale nevroblastomer hos barn, Nord. med. **36**:2504, 1947.

16. Cox, R. A.: Proptosis due to Neuroblastoma of Adrenal Cortex (Hutchinson's Syndrome): Report of Case, Arch. Ophth. **39**:731 (June) 1948.

17. Ryder, D. R.: Hutchinson's Syndrome, New Zealand M. J. **46**:415, 1947.

18. Larimer, R. C.: Neuroblastoma (Sympathogonioma) of Adrenal in Newborn Infant, J. Pediat. **34**:365, 1949.

19. Conference at the St. Louis Children's Hospital: Case 1, Neuroblastoma, J. Pediat. **32**:580, 1948.

20. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863-67, vol. 2, p. 150.

21. Dalton, N.: Infiltrating Growth in Liver and Suprarenal Capsule, Tr. Path. Soc. Lond. **36**:247, 1884-85.

22. Marchand, F.: Beiträge zur Kenntniss der normalen und pathologischen Anatomie der Glandula carotica und der Nebennieren, Internat. Beitr. z. Wissench. Med. Festschr. R. Virchow, Berlin **1**:535, 1891.

23. Pepper, W.: A Study of Congenital Sarcoma of Liver and Suprarenal, Am. J. Med. Sc. **121**:287, 1901.

adrenal gland, which he called lymphosarcoma, and it was not indicated to be of adrenal origin. From his description originated the so-called Pepper type, which indicated adrenal-hepatic tumor involvement. In 1907 Hutchinson [24] reported 10 cases (four of which were his own) of adrenal tumor with metastases to bones of the skull. Thus, the Hutchinson type became known and referred to the adrenal-skeletal distribution, the skeletal metastases being primarily in the skull. These types are no longer acceptable, since Farber [25] and Karsner [26] showed that the distribution of metastases bears no relation to cytological character or anatomical locations of the primary tumor. It was in 1910 that Wright [27] first described the distinguishing characteristics of the microscopic picture and used the term "neuroblastoma."

The neuroblastoma is classified as a neurogenic tumor, since it is now known to originate from the same cells as does the medulla of the adrenal gland, as well as portions of the sympathetic nervous system. Embryologically, the adrenal cortex is derived from the splanchnic mesoderm at the base of the dorsal mesentery, and patients with tumors arising from the cortex usually are adults and may show characteristic secondary sex changes. The medulla, however, originates from the ectoderm of the primitive neural crest. Two types of cells are found developing from the neural crest and are called sympathogonia. These cells may follow one of two routes in the process of differentiation, i e., they may become chromaffin cells of the adrenal medulla, or they may form the sympathoblast which finally becomes the sympathetic ganglion cell.

From these various tissues may result four distinct types of tumors: [28] the more embryonic sympathogonioma, the somewhat more differentiated but malignant neuroblastoma, the benign ganglioneuroma, and the chromaffinoma of the adrenal medulla. The neuroblastoma is the commonest of these tumors.

Since this tumor arises from these undifferentiated migratory cells, it may have its origin in widely varying parts of the body. Many, of course, arise in the adrenal gland itself, while many others arise from the sympathetic system anywhere from the cervical to the lumbar region. They have been known to arise from the organ of Zuckerkandl near the bifurcation of the aorta, as well as the celiac plexus. This variation in sites of origin naturally causes considerable variation in the clinical picture.

Grossly, this tumor varies greatly in size, and there is no correlation between size and metastases, as the smallest tumor may give rise to early widespread metastases. This tumor usually grows very rapidly, and is smooth and round, with a greenish-red color to the highly vascular, encapsulated surface. When the tumor enlarges, the surface becomes more nodular, and it breaks through the capsule. This naturally makes dissection at operation more difficult, as the

24. Hutchinson, R.: On Suprarenal Sarcoma in Children with Metastases to the Skull, Quart. J. Med. **1**:33, 1907-08.

25. Farber, S.: Neuroblastoma, read before the American Pediatic Society, May 3, 1940, abstracted in Am. J. Dis. Child. **60**:749 (Sept.) 1940.

26. Karsner, H. T.: Distribution of Metastases of Neuroblastoma of Adrenal, Tr. A. Am. Physicians **57**:209, 1942.

27. Wright, J. H.: Neurocytoma or Neuroblastoma, J. Exper. Med. **12**:556, 1910.

28. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, p. 427.

tumor may extend across the midline, or it may invade the adjacent structures, at times extending into the vertebra, causing pressure upon the spinal cord. The cut surface of the tumor is highly cellular and spongy and has a yellowish-gray color. Dark necrotic or hemorrhagic areas may be scattered throughout, especially in the larger tumors.

Microscopic examination of these tumors reveals a highly cellular structure showing evidence of rapid growth. The tumor cells are found in broad sheets and are similar in appearance to lymphocytes. There are many mitotic figures present in the spherical, multiple nuclei. The cytoplasm is clear. There are two characteristic features of this tumor that are diagnostic. First, there are groups of cells arranged into what has been termed a rosette, which has the nuclei of the cells arranged peripherally and the cytoplasm arranged centrally. Kato [29] felt this formation would better be called a pseudorosette, since there is no central canal. The other diagnostic finding is the development of neurofibrils that can be seen with the phosphotungstic acid hematoxylin stain. The fibrils are found in heaviest concentration in the central portion of the rosettes, as they are believed to arise from the tail processes of the cells forming these rosettes. A very small change in the state of development of these cells changes the picture to a sympathogonioma or a ganglioneuroma. In the former the cells are of a more embryonic nature, while the latter shows somewhat more differentiation.

Metastases may take place from the primary tumor in one of three ways. The commonest route is by direct extension, with lymphatic spread the next most frequent, direct invasion of the blood vessels being the least common route. In many cases there is only local metastases, but oftener there is also generalized metastases to the lungs, skeletal system, kidneys, and other organs. Metastases to the skull are the most frequent of the skeletal metastases. The long bones are frequently involved, and more rarely is there invasion of the flat bones.

DIAGNOSIS AND THERAPY

Neuroblastoma occurs equally in the two sexes. It is primarily a condition of infancy and childhood and is most frequently seen before the age of 5 yr. The tumor has been known to ocur in adults as well.

Since the primary neuroblastoma may originate in many different sites, the presenting complaint may be quite variable, and the patient may be first seen by various specialists, all of whom must be aware of this condition. The urologist may be faced with this problem, as in a case reported by Hepler [30] of a 3-week-old infant whose presenting complaint was anuria from the time of birth. A neuroblastoma was found obstructing urinary flow, and, with partial resection and roentgen therapy, the child was living and well four years later. Lee and Ritter [31] reported a case of a 5-mo.-old infant whose symptoms were the effect of adrenergic action and included marked excitability, perspiration, tachycardia, vomiting, and cardiac failure. A retropleural neuroblastoma was found at operation. The neuro-

29. Kato, K., and Wachter, H. E.: Adrenal Sympathicoblastoma in Children, with Special Reference to Biopsy of Sternal Marrow and of Metastatic Nodule in Skull, J. Pediat. **12**:449, 1938.

30. Hepler, A. B.: Presacral Sympathicoblastoma in an Infant Causing Urinary Obstruction, J. Urol. **49**:777, 1943.

31. Lee, W. E., and Ritter, J. A.: Intrathoracic Neuroblastoma, Ann. Surg. **117**:93, 1943.

surgeon also sees many cases, because of frequent involvement of the nervous system. Chandler and Norcross [32] presented four cases of tumors that eroded through the vertebra and involved the spinal cord. The orthopedist will occasionally see a case resulting from bony metastases and giving rise to pain or pathological fracture. The internist, ophthalmologist, and abdominal surgeon, as well as the pediatrician, will also be confronted with this problem. The tumor is rarely seen as a family occurrence, but Dodge and Benner [33] reported two cases in one family, the first child dying at the age of 4 yr. and the second at 7 mo.

Probably, the most frequent initial complaint is related to the abdominal enlargement. If pain is present, there are usually metastases present that are involving the retroperitoneal nerves or producing obstruction of the urinary or gastrointestinal tracts. There are the usual nonspecific findings of any tumor, including pallor, wasting, increasing fatigue or listlessness, progressive weight loss, and loss of appetite. The primary tumor may not be demonstrable, and the symptoms may result from metastases alone. When metastases are present, anemia usually is more marked, the temperature is elevated, the liver may be painful, and cough may result from pulmonary spread. Headache and vomiting, with other findings of increased intracranial pressure, may result from lesions in the brain, and proptosis, ecchymoses of the upper eyelid, and optic atrophy may be seen with retrobulbar involvement. The abdominal enlargement results from a palpable tumor, which may be smooth, but is oftener nodular and fixed, and may extend across the midline and be located at any level in the abdomen.

Laboratory aids in diagnosis may be helpful, but not infrequently they are inconclusive. The red-blood-cell count is usually low, and there is no change in the white-cell count. Urinalysis may show erythrocytes if the renal pelvis has been invaded. Roentgenograms of the abdomen may show an area of increased density in the region of the tumor, and, frequently, calcifications are present in the tumor. Studies of the bones may reveal skeletal metastases, and cranial roentgenograms may show separation of the sutures in younger patients. Bony destruction in the skull is characterized by radiating spicules perpendicular to the tables, described by Rypins [34] as "whiskers." The lungs and pleura may show miliary lesions. Pyelograms may show downward and lateral displacement of the homolateral kidney, but this will result from any mass located in this area.

Murray and Stout [14] studied the form and behavior of human tumors in vitro, and they included eight neuroblastomas. These tumors seemed to behave in a uniformly distinctive manner in vitro, and their difference from other tumors with which a neuroblastoma may be confused was so marked that use of tissue cultures is considered by these authors to be a most helpful diagnostic procedure. A positive diagnosis can be made in 24 hr. or less. When live tumor tissue from biopsy material is cultured in clotted plasma, two characteristic features are noted. First, typical neurites are produced by the cells. Secondly, there is necrosis of the outer

32. Chandler, F. A., and Norcross, J. R.: Sympathicoblastoma, J. A. M. A. **114**:112 (Jan. 13) 1940.

33. Dodge, H. J., and Benner, M. C.: Neuroblastoma of Adrenal Medulla in Siblings, Rocky Mountain M. J. **42**:35, 1945.

34. Rypins, E. L.: The Roentgen Diagnosis of Neuroblastoma in Children, Am. J. Roentgenol. **37**:325, 1937.

rim of the cells, and these cells also show affinity for neutral red when it is applied supravitally.

Another diagnostic procedure, which has been evaluated by Luhby and Diamond,[35] is bone-marrow aspiration. They indicated that when there is evidence of bone marrow metastasis, marrow examinations will be of value in making a positive diagnosis. This would be of little value in early diagnosis, however.

The differential diagnosis of neuroblastoma covers a wide field. Probably the commonest tumor that is likely to be confused with a neuroblastoma is embryonal carcinosarcoma (Wilms's tumor) of the kidney. This tumor occurs in about the same age groups, but it is usually larger, has a smooth surface, and is almost always limited to one side of the abdomen. Roentgen studies are of little value in differentiating these tumors, but calcifications are more frequent in neuroblastoma than in embryonal carcinosarcoma. Metastases from an embryonal carcinosarcoma go primarily to the lung and are rarely seen in bone. When skeletal metastases do occur, they are most likely to be found in the pelvis. Hematuria is rare and is a late occurrence in cases of embryonal carcinosarcoma.

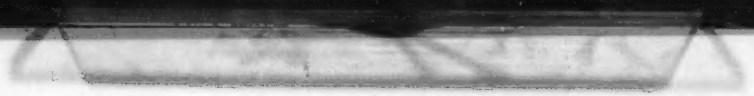
Other adrenal tumors may be confused with this tumor. The more embryonal sympathogonioma is difficult to diagnose, and a diagnosis of this tumor before death is rare. The benign ganglioneuroma is slower growing, encapsulated, and does not readily metastasize. The chromaffinoma, or pleochromocytoma, is usually a benign tumor that produces symptoms associated with the increase in production of epinephrine. Adrenal cortical tumors may also arise, and these are characterized by precocious sexual development of the patient.

Tumors with other sources may also be confused in making the diagnosis of neuroblastoma. Such tumors may arise from the ovary, but these tumors are very rare in this age group, and, when present, the tumor is usually freely movable and appears to arise from within the pelvis. Lymphosarcoma is usually associated with generalized superficial lymphadenopathy and the presence of ascites. Angioendothelioma (Ewing's tumor) is likelier to occur later in childhood and usually shows the typical roentgen picture of "onion peel" splitting of the periosteal layers. Barden [36] in 1943 thought that there was a definite similarity between angioendothelioma and neuroblastoma and that a differential diagnosis was very difficult. Scurvy, chloroma, and leukemia must be considered in the differential diagnosis. Scurvy will respond to usual antiscorbutic therapy, and chloroma and leukemia can usually be differentiated by peripheral-blood studies and bone-marrow examinations. Hand-Schüller-Christian disease occurs late in childhood, and there are the usual changes of splenic enlargement and the circular defects within the skull.

Treatment of the abdominal tumor with evidence of no widespread metastases is early abdominal exploration and complete removal of the tumor. If local extensions of the tumor make complete removal impossible, immediate roentgen therapy to the area of the tumor should be instituted. Since complete removal of the tumor

35. Luhby, A. L., and Diamond, L. K.: Neuroblastoma Metastases: Diagnosis by Bone Marrow Aspiration, with Note on Therapy with Radioactive Phosphorus and Nitrogen, Proc. Am. Federation Clin. Res. (1946) **3**:52, 1947.

36. Barden, R. P.: The Similarity of Clinical and Roentgen Findings in Children with Ewing's Sarcoma (Endothelial Myeloma) and Sympathetic Neuroblastoma, Am. J. Roentgenol. **50**:575, 1943.



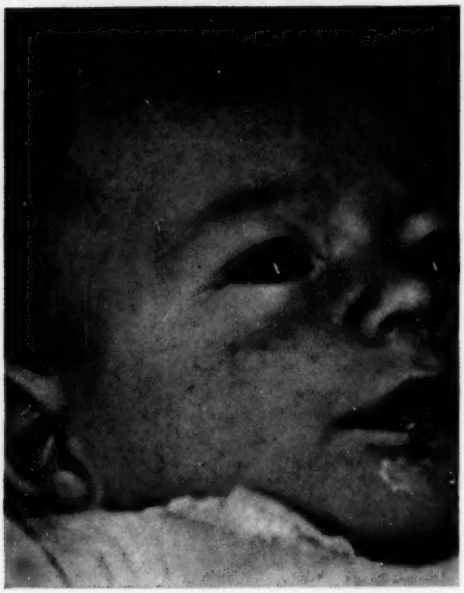


Fig. 1.—W. A., 9 weeks, before roentgen treatment for neuroblastoma, showing extreme comedos and infected pimples of acne, indicating androgenic activity.

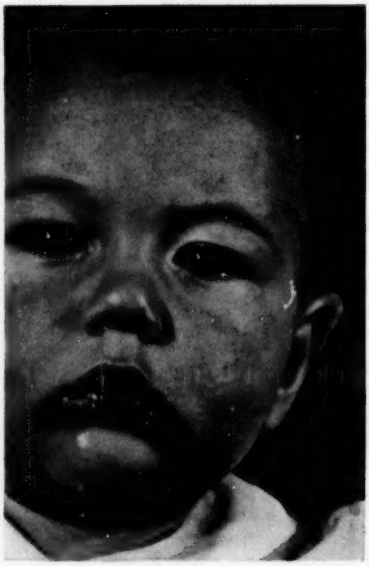


Fig. 2.—W. A., 10 mo., one month subsequent to the second course of roentgen therapy.

is highly improbable, roentgen therapy should follow all surgical procedures for this tumor, as the neuroblastoma cells are highly radiosensitive.

When generalized widespread metastases are present, diffuse roentgen therapy may be given, with close attention to the signs of depression of the bone marrow. Because of the high radiosensitivity, relatively small doses are needed. In 1950 Wittenborg [9] described in detail the roentgen therapy used in a large group of cases at the Children's Medical Center of Boston. Radioactive phosphorus and nitrogen mustard therapy may prove to be of value.[35] The course of patients with this tumor who have had no treatment or ineffective treatment is one of rapid failure and death usually within a few months. However, spontaneous hemorrhage into the tumor may occur and be followed by complete disappearance of the tumor without any treatment. Neuroblastomas have also been known to undergo spontaneous maturation to a benign ganglioneuroma. Cushing and Wolbach [37] reported a case of a neuroblastoma that was excised from the sixth dorsal level of the spine by McGuire, and 10 yr. later Cushing removed a recurrent tumor which was found to be a ganglioneuroma. The patient was finally reported well 35 yr. after the original operation. Also, adequate surgery and roentgen therapy may result in regression of the tumor and recovery, as the following case illustrates.

REPORT OF CASE

W. A., a white boy, was born normally on Nov. 4, 1944, and seemed to be in excellent condition. He was examined at the age of 3 weeks for occasional vomiting, and a solitary mass was felt 2 cm. below the left costal margin. Roentgen examination showed a questionable mass in the left upper quadrant of the abdomen, and the liver seemed larger than usual. A complete blood count gave normal results. A fasting blood-sugar level was 89 mg. per 100 cc., and after administration of 2 minims (0.12 ml.) of 1:1,000 ephedrine subcutaneously, it rose to 108 mg. per 100 cc. The result of the Wassermann test was negative. Cholesterol content of the blood was 222 mg. per 100 cc. The tuberculin reaction was negative to 0.01 mg. of old tuberculin. At the age of 9 weeks the mass in the left upper quadrant of the abdomen was more definite, and the infant's weight was 12 lb. (5,440 gm.). The measurements were head circumference 38 cm., chest circumference 37 cm., and abdomen circumference 47 cm., a gross enlargement of the latter. At this time he was admitted to the hospital [38] with marked abdominal distention resulting from a liver so enlarged that it extended 8 cm. below the costal margin and with the left upper quadrant mass extending 7 cm. below the costal margin. Comedos and acne, with small infected pimples, were present over the cheeks, and this was probably due to stimulation of sex hormones (Fig. 1). The hemoglobin level was 11.2 gm., erythrocytes 4 million, and leucocytes 11,100, per cu. mm. The differential count showed 33% polymorphonuclear leucocytes, 4% eosinophiles, 50% small lymphocytes, and 7% mononuclear cells. The phenolsulfonphthalein kidney-function test showed 35% excretion in the first hour and 15% in the second hour. Laboratory data were blood van den Bergh test, negative results; icterus index, 5 mg. per 100 cc.; blood nonprotein nitrogen, 30 mg. per 100 cc.; fasting blood sugar, 72 mg. per 100 cc., and sugar level following administration of 2 minims of 1:1,000 ephedrine, 77 mg. per 100 cc. Urinalysis gave normal results, and the stools showed a 3+ guaiac reaction.

Roentgen examination of the chest showed normality except for moderate elevation of the left diaphragm. Flat roentgenograms of the abdomen revealed only slight increase in density in the upper part of the abdomen, with downward displacement of the intestines. Intravenous pyelograms showed no excretion of dye into the right kidney. The left kidney was visualized and appeared normal. Examination of skull and long bones showed no abnormalities.

37. Cushing, H., and Wolbach, S. B.: The Transformation of a Malignant Paravertebral Sympathicoblastoma into a Benign Ganglioneuroma, Am. J. Path. 3:203, 1927.

38. The patient was referred by Dr. Ruth Kraft, Detroit.

A biopsy disclosed a tumor of the left adrenal gland. Sections from bits of tissue removed showed dense, pink-staining, sparsely nucleated stroma supporting large masses and columns of deeply staining oval or round cells. These had little cytoplasm, but the nucleus was hyperchromatic. There was a tendency toward whorl formation in some places, but no typical

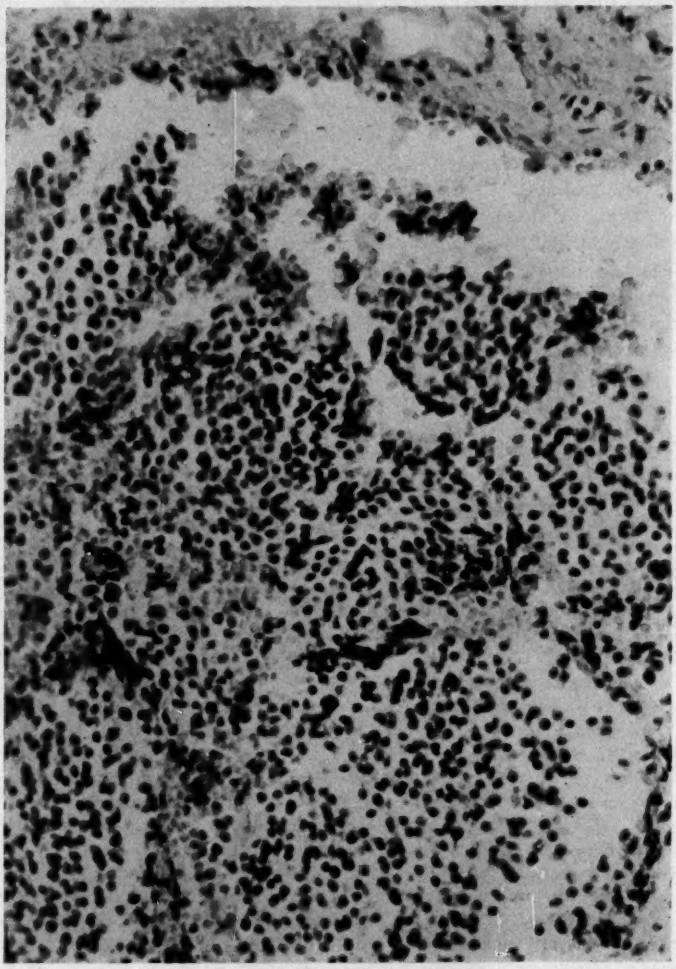


Fig. 3.—Biopsy section. The diagnosis was malignant neurocytoma of the left adrenal gland.

rosettes were found. The diagnosis was malignant neurocytoma of the left adrenal gland[39] (Fig. 3).

Immediate roentgen therapy was begun, and the patient was given 20 treatments in 38 days, delivering an estimated dose of 1,400 r to the tumor site in the upper part of the abdomen.

39. The pathologic study was done by Dr. F. W. Hartman, Department of Pathology, Henry Ford Hospital.

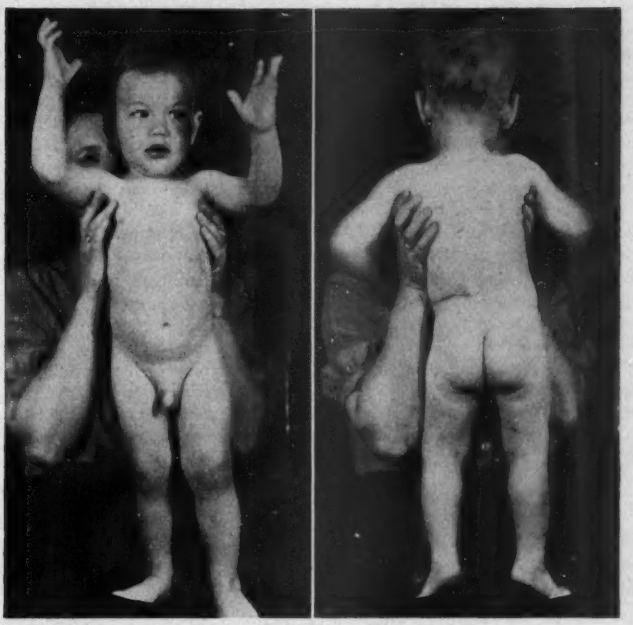


Fig. 4.—W. A., 3½ yr., front and back view.

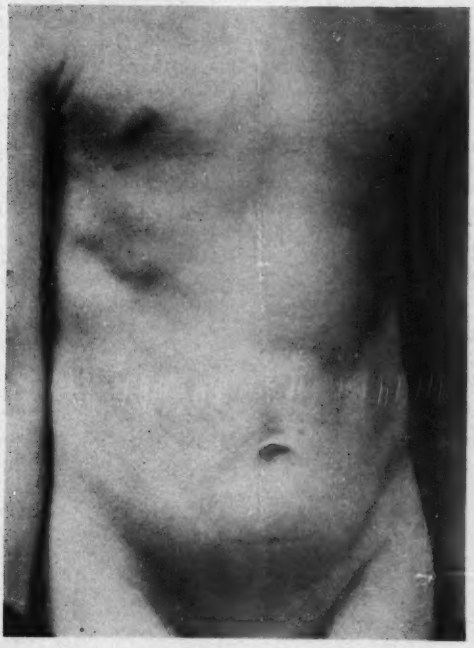


Fig. 5.—W. A., 6 yr., showing normal development. He is in school and seems normal.

Two months after the first course he was given a second course, consisting of 16 treatments in 20 days delivering to the abdomen an estimated dose of 1,250 r. The factors for the roentgen therapy were 200 kvp., 50 cm. distance, 25 ma., half-value layer 1.0 mm. cu. The field size varied from 8 by 10 cm. to 15 by 15 cm. The patient's skin remained in good condition, and he improved generally. By July 28, 1945, one month after roentgen therapy was given, the liver had receded to the costal margin, but a small, firm mass could still be felt in the left upper quadrant of the abdomen (Fig. 2). At the age of 11 mo. he weighed 19 lb. (8,620 gm.) and seemed well. At the age of 14 mo., the mass in the left upper quadrant could no longer be felt and the liver was of normal size. At 18 mo. complete roentgen study was made of all long bones and the skull for possible metastases, and the only finding was "a suggestion of several calcified glands in the upper abdomen." At the age of 2 yr. this patient was a happy, normal boy eating a regular diet and showing no evidence of any recurrence.

In August, 1948, at the age of 3½ yr. (Fig. 4), a small, indistinct, firm mass was palpable in the upper part of the abdomen just below the xiphoid. The left lobe of the liver was palpable and smooth. He was readmitted to the hospital at that time for retrograde pyelography. This revealed the left kidney to be lower than the right, but no evidence of a tumor was seen. However, with the presence of a palpable mass and displacement of the kidney, a third course of roentgen therapy was given. This consisted of 13 treatments in 16 days delivering an estimated dose of 1,400 r to the tumor. The patient has been in good health to the present time, was last seen in July, 1951, and is known to be well. Development is normal at this time, and there is no mass palpable, nor is the liver enlarged (Fig. 5).

SUMMARY

A report of the number of cases to date in the literature is given, with particular attention to those cases in which the patients have survived. It is important to note that 10% of all reported cases are reported as "cures."

A review of the history, pathology, methods of diagnosis, and therapy is presented.

The importance of early diagnosis and adequate treatment leading to a more favorable prognosis is stressed.

A case of neuroblastoma in a 3-mo.-old infant is presented. The patient is living and well six years after diagnosis and treatment.

Case Reports

SERUM-SICKNESS-LIKE SYNDROME FROM PENICILLIN

JOSEPH H. LAPIN, M.D.
AND
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BRONX, N. Y.

WE ARE reporting two cases of a serum-sickness-like syndrome in children which seemed to be due to penicillin used in therapy. In both cases, there was a pronounced encephalitic appearance, and in both electrocardiographic studies showed myocardial changes; in one, an "allergic" glomerulonephritis resulted, and in the other, suspicion-arousing urinary findings.

REVIEW OF LITERATURE

Although reactions to penicillin were reported very early,[1] the number of such reports has become so large that many physicians are justifiably wary of using the drug indiscriminately. To date only five deaths have been reported.[2] A comprehensive review[3] lists all the possible varieties, most of the reports being of simple allergic reactions such as urticaria, sneezing, wheezing, and exfoliative dermatitis, but even Herxheimer reactions in nonsyphilitics[4] and Loeffler's syndrome have been noted. Reports of a serum-sickness-like reaction are by now numerous,[6] but case reports in the pediatric literature are notable by their absence.

From the Pediatric Service of the Bronx Hospital.

1. (*a*) Cormia, F. E.; Jacobsen, L. Y., and Smith, E. L.: Reactions to Penicillin, Bull. U. S. Army M. Dept. **4**:694 (Dec.) 1945. (*b*) Cormia, F. E., and Lewis, G. M.: Experimental Aspects of Sensitization with Special Reference to Conjoint Sensitization to Superficial Fungus Disease, J. Invest. Dermat. **7**:375-380 (Dec.) 1946. (*c*) Wilensky, A. O.: Fatal Delayed Anaphylactic Shock After Penicillin, J. A. M. A. **131**:1384 (Aug. 17) 1946.

2. (*a*) Wilensky.[1c] (*b*) Barksdale, E. E., in discussion on Morginson, W. J.: Toxic Reactions Accompanying Penicillin Therapy, J. A. M. A. **132**:915-919 (Dec. 14) 1946. (*c*) Waldbott, G. L.: Anaphylactic Death from Penicillin, ibid. **139**:526-527 (Feb. 19) 1949. (*d*) Rabinovitch, J., and Snitkoff, M. C.: Acute Exfoliative Dermatitis and Death Following Penicillin Therapy, ibid. **138**:496-498 (Oct. 16) 1948. (*e*) Berne, R. M.: An Unusual Reaction to Penicillin, New England J. Med. **242**:814-817 (May 25) 1950.

3. Brown, E. A.: Progress in Allergy: Reactions to Penicillin; Review of Literature, 1943-1948, Ann. Allergy **6**:723-746 (Nov.-Dec.) 1948.

4. Barksdale, E. E.; Frost, D. M., and Nolon, J. J.: Reactions from Penicillin with Case Report of 1 Fatality, U. S. Nav. M. Bull. **48**:883 (Nov.-Dec.) 1948.

5. Footnote deleted.

6. (*a*) Strazza, J. A., Jr.: Delayed Sensitization Similar to Serum Sickness, J. A. M. A. **130**:1071 (April 20) 1946. (*b*) Gordon, E. J.: Delayed Serum Sickness Reaction, ibid. **131**:727-730 (June 29) 1946. (*c*) Kolodny, M. H., and Denhoff, E.: Reactions in Penicillin

(Footnote continued on next page)

The reason for the infrequency of allergic reactions in infants and children is probably [1] the comparative rarity of Trichophyton infections in children; hence "id" reactions are practically unknown in this age group. Some 5% of the general population [7] have been found allergic, but of the 65 children tested by Peck and his co-workers [8] none showed a spontaneous reaction, as compared with 5.4% of the adults tested by them.

Passive transfer of drug hypersensitivity is almost uniformly unsuccessful, as could be postulated from the fundamental work of Landsteiner.[9] The striking similarity between so-called drug fever and serum sickness was first noted [10] with sulfonamide reactions. The incubation period of four to 13 days, the abrupt onset with malaise, nausea, and itching, the variations in febrile response from normal to 106 F., and the average duration of fever of two to four days are all quite similar to the clinical characteristics of serum sickness. However, the fundamental difference between drug sensitivity and serum sickness in regard to the role of antibodies and the success of passive transfer in true serum sickness must be emphasized. It is for this reason that the work of Rich and his associates [11] in the production of lesions resembling periarteritis nodosa in the arterial walls of animals by means of injections of foreign proteins and also by sulfonamide therapy has proved so attractive in producing a working theory of the similarity between the clinical pictures of true serum sickness and so-called drug fever. Whether or not

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Therapy, ibid. **130**:1058-1061 (April 20) 1946. (*d*) Rosellini, L. J., and van Rooy, C. W.: Delayed Allergic Reaction to Penicillin in Oil and Wax Treated with Procaine Intravenously, Northwest Med. **45**:849-850 (Nov.) 1946. (*e*) Eisenstadt, W. S.: Hypersensitivity Simulating Serum Sickness, Minnesota Med. **29**:689 (July) 1946. (*f*) Truitt, G. W.: Reactions to Penicillin, Ann. Allergy **4**:196-198 (May-June) 1946. (*g*) Vogel, H. R.: Reactions to Penicillin, Arch. Dermat. & Syph. **54**:713-714 (Dec.) 1946. (*h*) Morginson, W. J.: Reactions Accompanying Penicillin Therapy, J. A. M. A. **132**:915-919 (Dec. 14) 1946. (*i*) O'Donovan, W. J. and Klorfajn, I.: Sensitivity to Penicillin: Anaphylaxis and Desensitization, Lancet **2**:444-446 (Sept. 28) 1946. (*j*) Strakosch, E. A.: Serum Sickness-Like Reactions, Rocky Mountain M. J. **43**:558-560 (July) 1946. (*k*) Mendel, T. H., and Prose, P. H.: Severe Allergic Reactions, Am. J. M. Sc. **212**:541-545 (Nov.) 1946. (*l*) Wilkenson, A. J., and Zinneman, K.: Allergy with Symptoms of Serum Sickness, Brit. M. J. **2**:865-866 (Nov. 29) 1947. (*m*) Reid, J. O.: Angioneurotic Edema as Possible Sequel to Administration, Brit. M. J. **2**:870 (Nov. 29) 1947. (*n*) Kendig, E. L., Jr., and Toone, E. C., Jr.: Delayed Serum Type of Reaction to Penicillin: 3 Cases in 1 Family, South. M. J. **40**:697-698 (Aug.) 1947. (*o*) Walley, J. F. L.: Severe Reaction After Penicillin, Brit. M. J. **1**:150 (Jan. 24) 1948. (*p*) Burleson, R. J.: Anaphylactic Shock Due to Penicillin, J. A. M. A. **142**:562-563 (Feb. 25) 1950. (*q*) Felder, S. L., and Felder, L.: Unusual Reaction to Penicillin, ibid. **143**:361-362 (May 27) 1950.

7. (*a*) Rostenberg, A., Jr., and Welch, H.: Studies of Types of Hypersensitivity Induced by Penicillin, Am. J. M. Sc. **210**:158-167 (Aug.) 1945. (*b*) Gottschalk, H. R., and Weiss, R. S.: Epidermal Sensitivity to Penicillin, Arch. Dermat. & Syph. **53**:365-371 (April) 1946.

8. Peck, S. M.; Siegal, S.; Glick, H. W., and Durtin, A.: Clinical Problems in Penicillin Sensitivity, J. A. M. A. **138**:631-640 (Oct. 30) 1948.

9. Landsteiner, K.: The Specificity of Serological Reactions, Springfield, Ill., Charles C Thomas, Publisher, 1936.

10. Hageman, P. O., and Blake, F. G.: A Specific Febrile Reaction to Sulfanilamide, J. A. M. A. **109**:642-646 (Aug. 28) 1937.

11. Rich, A. R.: Role of Hypersensitivity in Periarteritis Nodosa, as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123-140 (Sept.) 1942.

one accepts the viewpoint of Rich, the widespread character of the symptoms in cases such as the two presented here forces us to assume a very extensive involvement of tissues all over the body. In such cases the encephalitic picture might be explainable by edema of the brain, the findings of myocardial damage could be attributed to Aschoff-like bodies in the myocardium [12] or edema and diffuse infiltrations, and the glomerular nephritis ascribed to allergic sensitization of the glomeruli.

The pathology of fatal cases is illustrated by a recent autopsy report [2c] on a 53-yr.-old man who experienced an erythematous and bullous eruption, with marked edema of the face, hands, and feet. Later, exfoliative dermatitis and a purpuric and urticarial eruption appeared and the patient presented peritonitis with large subcutaneous hemorrhages. The localization of the pathologic lesions was in the skin and intestinal tract, both arteries and veins showing areas of necrosis with a marked cellular reaction. However, in contradistinction to the usual findings in serum and sulfonamide reactions (Rich) there was in this case a primary involvement of the veins in early lesions.

REPORT OF CASES

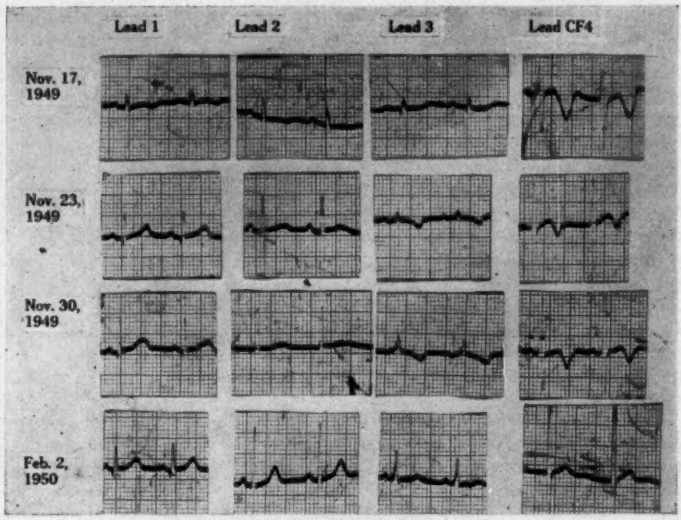
CASE 1.—M. S., a 4-yr.-old boy, who had been well until 21 days before admission, March 13, 1949, when he had been given penicillin orally for an upper respiratory tract infection. The maternal grandfather had hay fever and asthma, and the patient had had allergic gastrointestinal reactions until 14 mo. of age. Five days before admission, a rash was noted on his hands and he complained of itching on the soles. Three days before admission, he had a slight fever again, for which he was given more penicillin orally. After this, he began to have a widespread urticarial eruption, sometimes nummular, sometimes marginated, all over the body, and his fever became septic, with wide temperature swings up to 105 F. A dermatologist made a diagnosis of erythema multiforme, and prescribed 50 mg. of tripelennamine (pyribenzamine®) hydrochloride every three hours. After 24 hr., the child became drowsy, disoriented, and sometimes wildly delirious, and had occasional strychninelike convulsions. On admission he seemed acutely ill, with a generalized urticaria, most marked on the extremities, back, and buttocks, somewhat enlarged cervical nodes on the right side, a temperature ranging from 104 to 105.8 F., mild stomatitis, slight pharyngitis, delirium, and occasional convulsive episodes. The white cell count was 21,200, with 68% segmented forms, 29% lymphocytes and 3% mononuclears. The spinal fluid, blood culture, and roentgenogram of the chest were completely noncontributory. The urine showed a few coarse granular casts, a rare red blood cell, and two to three white cells per high-power field, and gave a 1 + reaction for albumin. Treatment consisted of small doses of epinephrine every hour, alcohol sponges, and clyses. The child vomited four times within the first 24 hr., and the temperature dropped by lysis, becoming normal on the fourth hospital day. The urticarial rash, the pharyngitis, the stomatitis, the delirium, and the convulsive episodes were all gone by the third day.

Progress Report.—After the patient had been discharged from the hospital, a persistent tachycardia ranging from 110 to 130 together with a short blowing systolic murmur of moderate to faint intensity developed. The murmur was best heard at the left sternal margin between the third and fourth interspaces, exaggerated in the reclining position, and diminished on inspiration.

An electrocardiogram, recorded on March 26, 1949, showed a P-R interval of 0.17 sec.; tracings taken on April 18 and April 26, 1949, showed a P-R interval of 0.13 sec. There were no significant T-wave changes in any of the tracings. The shortening of the P-R interval (with no change in the heart rate) is suggestive of subsiding myocardial damage. Since then, the tachycardia and murmur have both disappeared. Observation for the next 14 mo. has shown a normal development, with no signs of cardiac or kidney involvement.

12. Hytmancik, M. R.; Schofield, N. D., and Herrmann, G. R.: Allergic Cardiovascular Disease, with Report of 2 Cases of Periarteritis Nodosa, Am. J. M. Sc. **217**:187-193 (Feb) 1949.

CASE 2.—T. P., a 5-yr.-old boy, was admitted Nov. 10, 1949, with a history of fever for five days, with temperatures up to 104 F., and a discrete macular eruption on the legs and arms. Medication had consisted of penicillin orally and intramuscularly administered and several oral doses of aureomycin. On admission, the only findings were enlarged posterior cervical nodes and generalized abdominal tenderness, with occasional urticaria and an erythematous rash over the arms and legs. The white blood cells were 19,100, with 53% segmented forms, 37% stab forms, 4% monocytes, and 4% eosinophiles. Urine revealed 7 to 10 pus cells, few pus casts, and a moderate number of granular casts. Urea nitrogen was 36.7 mg. per 100 cc., and carbon dioxide-combining power 40 vols. per cent. Spinal fluid, blood cultures, and roentgenograms of skull, chest, and abdomen were all negative. Oliguria, signs of cardiac failure, and generalized edema and rales at the bases of the lungs appeared within the first 48 hr. but disappeared as the temperature came down to normal by the sixth hospital day. At this time, drowsiness, failure of the pupils to respond to light, marked weakness of both legs, hyperesthesia, and slight nuchal rigidity were noted.



Electrocardiograms in Case 2.

Agglutination tests for rickettsialpox, typhoid, typhus and brucellosis were negative. The child continued to have 3 to 5 pus cells, occasional red cells, and a few granular casts in all urine specimens. The temperature became normal by the sixth day; the neurological signs disappeared by the twelfth day, and the rash faded completely by this time. The child was readmitted two months later for evaluation of cardiac and kidney damage. Only a systolic murmur of moderate intensity at the apex was found. Results of urinary studies, including Fishberg concentration and dilution tests, were normal. The gastrointestinal roentgenograms showed a questionable spasm of the duodenal bulb. Roentgenograms of the chest, barium enema roentgenograms, and blood urea nitrogen were normal. A series of electrocardiograms (Figure) definitely supported the diagnosis that an acute myocardial disease was present. Over the course of weeks the heart returned to normal. A tracing taken one week after admission, on Nov. 17, 1949, showed abnormally low voltage in the limb leads. The T wave in leads I, II, and CF4 was inverted. This record was definitely abnormal and indicated acute myocardial damage. Subsequent tracings on Nov. 23 and Nov. 30, 1949 showed changes to a more normal pattern. The voltage in the limb leads had increased to normal, and the T wave in

leads I and II had become upright, while the T wave in lead CF4 was less deeply inverted. Two months later, on Feb. 2, 1950, a tracing showed the T wave to be upright in all leads and the tracing was normal in all other respects.

In acute glomerulonephritis it is not uncommon for the voltage in the limb leads to decrease and the T wave to become inverted in lead I and more upright in lead III, as was the case here.

TREATMENT

At first, the use of epinephrine by injection and of antihistaminics seemed the logical method of approach, but the failure of many patients to respond led to further experimentation. The use of procaine hydrochloride intravenously [13] has been extolled, but the possibility of death from sensitization to the procaine or from its effect on cardiac rhythm cannot be ignored. At the time of treatment corticotrophin (ACTH) was not available, but Bardley and his co-workers [14] reported that 25 mg. given every six hours for the first two days and then in a lower dosage produced a striking improvement within six to eight hours in all patients with severe penicillin sensitivity reactions of fever, arthritis, and giant urticaria, and complete cessation of these reactions in 36 hr.

RECOMMENDATIONS

The following recommendations for prevention of penicillin reaction are to be found in the literature [2c]: (*a*) An inquiry should be made into the history of serum sickness. (*b*) Intradermal tests should be performed if there is any suspicion of sensitivity, although such tests may be unreliable. (*c*) For any allergic patient who has had previous injections of penicillin, intradermal injections should be prescribed, at first, of only 100 to 300 units, rapidly building up to required dose. (*d*) Intravenous therapy should be restricted to desperate cases. (*e*) Precautions should be taken to avoid accidental intravenous administration by always withdrawing the plunger of the hypodermic syringe before injecting.

Cormia [1a, b] and others [15] feel that testing for penicillin sensitivity before administration of the drug has been neither reliable nor practical. In view of the unsatisfactory experiences with skin testing for idiosyncrasies to other drugs, such as salicylates and gold, we feel that there is no substitute at present for constant observation of each patient who is given these allergenic drugs. Hansel [16] finds the reaction of the individual patient to any type of preparation unpredictable. Sensitivity may rapidly disappear or may gradually decrease over a period of six months to a year, or it may heighten with each subsequent attack.

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13. (*a*) Dressler, S., and Dwork, R. E.: Procaine Hydrochloride Intravenously in Treatment of Reactions Similar to Serum Sickness, J. A. M. A. **133**:849 (March 22) 1947; Correspondence, ibid. **133**:1301 (April 26) 1947. (*b*) Cohen, A. E., and Kaufman, J.: Use of Procaine Hydrochloride Intravenously in Treatment of Reactions to Penicillin: 4 Cases, J. Allergy **19**:68-70 (Jan.) 1948.

14. Bardley, J. E.; McGehee, H. A.; Howard, J. E., and Newman, E. U.: Preliminary Report on the Use of ACTH in the Hypersensitive State, Proc. First Clinical ACTH Conference, 1950, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, pp. 469-478.

15. Mendell, T. H., and Prose, P. H.: Severe Allergic Reactions to Penicillin, Am. J. M. Sc. **212**:541-545 (Nov.) 1946.

16. Hansel, F. K.: Penicillin Sensitivity, Ann. Allergy **7**:619-624 (Sept.-Oct.) 1949.

COMMENT

We have been unable to find in the pediatric literature any reports of cases such as the two we have presented. Both patients were allergic children; after an incubation period varying from four to 21 days, a serum-sickness-like reaction to penicillin occurred, with temperatures ranging from normal to 105.8 F., an encephalitic appearance with delirium and convulsions, electrocardiographic findings strongly suggestive of myocarditis, and urinary findings confirming a glomerular nephritis in one and suggestive in another. Since such reactions are by no means uncommon in adults [6h] and since theoretical considerations make such reactions at least possible in view of Rich's work, we feel that no further tests were necessary. At the time, we attempted passive transfer of the penicillin sensitivity to other patients unsuccessfully but did not try to elicit a positive skin reaction to penicillin. Since these children had already suffered such widespread damage to their vascular-collagen system, it was felt that even skin testing could, theoretically at least, elicit a fatal response. In addition, a negative skin test would not be conclusive.[3] It should be noted that a year's follow-up in both cases showed the transitory nature of the damage, at least as far as we can judge now. The central nervous system is perfectly normal, the electrocardiogram is normal, and results of kidney-function tests in both children are completely normal.

SUMMARY

Although it is true that the vast majority of penicillin reactions are mild, fatalities have occurred, even if rarely. Two cases are presented of children who showed an encephalitic syndrome with myocarditis and nephritis, presumably on an allergic basis, as well as the usual urticaria, angioneurotic edema, and fever. A summary of the literature is presented to show the theoretical basis for such reactions, the infrequency in children due to the rarity of Trichophyton infection is pointed out, and recommendations for both prophylaxis and treatment are made.

ECTODERMAL DYSPLASIA, ACHONDRODYSPLASIA, AND CONGENITAL MORBUS CORDIS

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IN THE tenth edition of the Holt-McIntosh "Diseases of Infancy and Childhood" [1] a curious case is mentioned of a girl aged 4 yr. with stunted growth, supernumerary digits, and squint. The four members were too short for the size of the trunk; each hand had six fingers with hypoplastic nails, and the feet were similarly malformed. The hair was rather fine; the eyebrows and eyelashes were normal. The teeth were cone-shaped. The sweat and sebaceous glands functioned normally. The basal metabolic rate was +35%. Roentgen examination showed brachydactylia and chondrodysplasia but no signs of congenital deformity of the heart.[2]

Ellis [3] in 1940 presented the description of a girl aged 20 mo. whose nails were defective and whose teeth erupted late and were also defective. The hair was fair and sparse and the skin dry and scaly. The limbs were too short, the proximal segments being more reduced in length than the distal ones, but there was no real dwarfism. On each hand were six digits. Roentgenologically the long bones resembled the bones of a patient with achondroplasia, with exostosis in the hip region and chondrodysplasia of the hands. The heart shadow was enlarged, and the signs and symptoms of congenital localized septal defect—Roger's disease—were found.

In the same issue of the *Archives of Diseases in Childhood* van Creveld presented his observations on a boy aged 4 yr. with polydactyly of the hands; congenitally malformed teeth and nails; fair, fine scanty hair, and dry scaly skin. The boy had short limbs, with chondrodysplasia in the hands and feet. In this case also symptoms of Roger's disease were noted.

Thus in three children of different sexes and races there was observed a new syndrome consisting of (1) osseous deformities resembling the picture of achondroplasia with exostosis and peripheral chondrodysplasia; (2) polydactyly; (3) ectodermal defects affecting nails, teeth and hair, and (4) in all but the first case a congenital cardiac defect. This syndrome now bears the names of Ellis and van Creveld.

1. Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, ed. 10, revised by L. E. Holt, Jr., and R. McIntosh, New York, D. Appleton-Century Company, 1933.

2. Brailsford, J. F.: The Radiology of Bones and Joints, ed. 4, Baltimore, Md., Williams & Wilkins Company, 1948, p. 29.

3. Ellis, R. W. B., and van Creveld, S.: A Syndrome Characterized by Ectodermal Dysplasia, Polydactyly, Chondro-Dysplasia and Congenital Morbus Cordis: Report of 3 Cases, Arch. Dis. Childhood **15**:65-84, 1940.

4. Keizer, D. P. R.: Dysostosis mandibulofacialis (Franceschetti-Zwahlen), Nederl. tijdschr. v. geneesk. **94**:1195, 1950.

It is of interest to note that two of the three patients were born of parents who were first cousins but who had no congenital deformities whatever.

We had the opportunity to study in our clinic a curious case of congenital malformations resembling in several particulars the Ellis-van Creveld syndrome.

REPORT OF A CASE

W. Sch., a woman aged 21, since birth has presented curious deformities which have led to several examinations. Her parents are healthy, without hereditary defects and not consanguineous. Inquiries regarding the mother's pregnancy and diseases during the first months of pregnancy brought no significant information.

Fig. 1.—Photograph of the patient, showing the sparse hair, heavy eyebrows and eyelashes, prognathous jaw, and malformed hands.

The patient is a very healthy woman of good intelligence; she is rather small, with a height of 155 cm. and a weight of 56.6 kg. Her limbs are too short for the trunk, and the proximal segments are especially reduced in length. She stands with distinct lordosis, genua valga and pedes planovalgi. All movements are executed without complaint. The joints are normal, and the muscle strength is extraordinarily good. No disturbances in sensibility could be found. The reflexes are normal. Her only complaint after executing motions for some time is of backache, due to the excessive lordosis.

The skull is rather small, dolichocephalic and covered with fine, dark, sparse hair, all broken off at a distance of 5 cm. from the skull (Fig. 1). The eyebrows and eyelashes are much too heavy; the brows are connected over the bridge to the well pronounced aquiline nose. The ears

are too large, and the lower jaw shows distinct prognathism. The teeth are too small, resembling mouse teeth, and incline backward; there is no sign of decay or of structural defects.

Fig. 2.—Photograph of the patient's feet and legs.

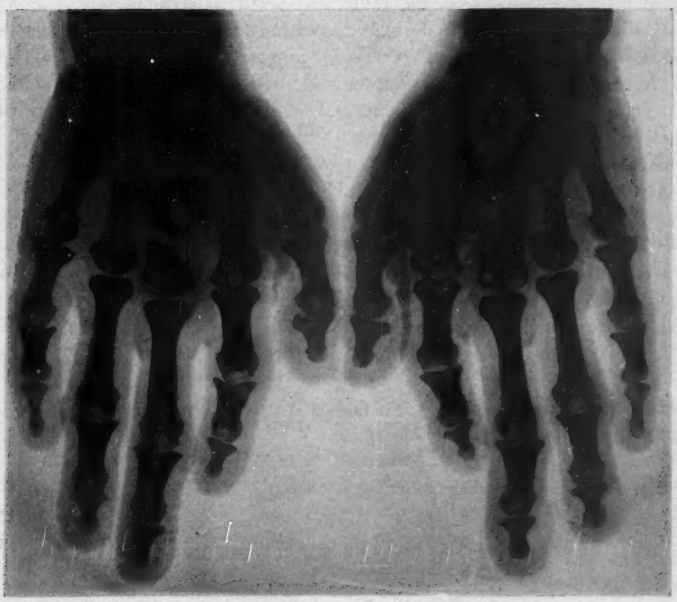

Fig. 3.—Peripheral dyschondroplasia of hands.

A distinct goiter can be palpated; the consistency is soft, and vessel tones can be heard on auscultation of the goiter. The blood pressure is 130/60, the pulse rate 100 a minute, and the basal metabolic rate +25%. The skin perspires freely and feels soft except on the extensor surfaces of the arms and legs, which are ichthyotic (Fig. 2).

The thorax is free from malformations. The outline of the heart seems to be enlarged to percussion, especially to the right side, and the beat is heaving. On auscultation a scraping systolic murmur can be detected to the left of the sternum in the fourth interspace. The roentgenogram shows distinct enlargement to the right.

In the abdomen there were no detectable abnormalities. Secondary sex characteristics are present and normal. The menarche was established at the age of 12 yr., and menses are now normal. The pelvis is flat.

The limbs are too short in comparison with the trunk, owing partly to reduction in length of the proximal segments and partly to malformations of the feet and hands—brachydactyly with deformations of the phalanges in the region of epiphysial lines. The finger and toe nails are like thin white scales, torn and destroyed by the slightest trauma. The fourth toe of each foot is abnormally short and overrides the third toe (Fig. 2).

Roentgen examination of the whole skeleton revealed that the skull is small but well proportioned, with a small sella turcica. The spine is straight with high vertebral bodies and small intervertebral disks, even between the first and second and the second and third lumbar vertebrae. The spinous processes are pointed like knives, and on the right side of the ninth and tenth thoracic vertebrae are exostoses. The hands and feet show peripheral dyschondroplasia only (Fig. 3).

COMMENT

The following abnormalities were observed in our patient: (1) osseous deformities superficially resembling achondroplasia—short limbs and lordosis, peripheral chondrodysplasia in the hands and feet with shortening of the fourth digit, high vertebral bodies, exostoses on the ninth and tenth thoracic vertebrae and prognathous lower jaw; (2) ectodermal dysplasia—broken-off hairs, mouse teeth, dysplasia of the nails and ichthyosis; (3) congenital localized ventricular septal defect, Roger's disease, and (4) symptoms of slight thyrotoxicosis. One important clinical feature, polydactyly, is lacking, and additional, less obvious malformations such as congenital fusion of the capitate and hamate bones and ectopia of the proximal ossification center of the tibia observed by Caffey in all the published cases and in one unpublished case could not be found in this patient. Unlike McIntosh's patient, in whom the congenital cardiac defect was lacking, in our patient the polydactyly and the less obvious malformations were missing.

It seems that in the Ellis-van Creveld syndrome, just as in dysostosis mandibulofacialis (Franceschetti-Zwahlen) both complete forms and incomplete forms (formes frustes) must be recognized.

SUMMARY

A case of a forme fruste of the Ellis-van Creveld syndrome in a woman aged 21 is reported.

Progress in Pediatrics

CONGENITAL MICROCOLON

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AND
LIEUTENANT R. W. SHARP (MC), U.S.N.

ATRESIA and stenosis of the colon are the rarest of all congenital narrowings of the gastrointestinal tract. Although this paper is concerned chiefly with congenital stenosis of the colon, these lesions are so clearly related to similar occlusions elsewhere in the intestinal tract in the matter of symptomatology, therapy, and probable etiology that reference to allied disorders situated elsewhere in the bowel can scarcely be avoided. Congenital intestinal atresia and stenosis are associated with a high mortality, but considering this group of developmental abnormalities as a whole, one finds reports of an increasing number of successfully treated patients appearing in the literature. These successes, all resulting from wisely chosen, properly timed, and carefully executed surgical procedures, have enhanced the importance of an early diagnosis for infants suffering with defects of this type. Prompt recognition of the obstruction and early surgical relief offer the only hope for a favorable outcome. As suggested by Rolens,[1] the case to be described herein is being reported not only because of its rarity but also in order to invite attention again to the fact that such anomalies do occur and to emphasize that many congenital intestinal occlusions are amenable to surgical therapy. In addition, a new but as yet untried method as an approach to an unsolved surgical problem, that of congenital microcolon, will be suggested.

The terms atresia, stenosis, and microcolon in reference to congenital narrowings of the colon have been applied in the literature in a manner that is somewhat confusing. In some instances the terms have been used interchangeably. It is thus difficult to determine with any exactitude the true incidence of any one of this group of lesions. Although total obliteration of the colon does occur, congenital segmental narrowings are seen, and complete agenesis of segments of the large bowel have been encountered, none of these terms are synonymous with congenital microcolon.

In the case described below there was certainly a high degree of stenosis, and, from a functional standpoint, an atresia in fact existed. We have chosen the term microcolon as most applicable, however, because it best describes the gross appearance of the colon, that is, an abnormally small colon from the cecum to the rectum. Furthermore, that designation most accurately describes a colon in which all coats of the bowel were present in all areas and one that presented a lumen throughout,

From the U. S. Naval Hospital, Corpus Christi, Texas (Captain Storey, formerly Chief of the Surgical Services, Lieutenant Sharp, formerly on the Medical Service).

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1. Rolens, M. E.: Atresia of the Colon, J. Nat. Proct. A. **18**:57 (Feb.-March) 1946.

even though it was one of almost microscopic size and completely occluded. Greig's statement that "in congenital microcolon, the viscus is a colon in miniature" [2] applies perfectly to our case.

REPORT OF CASE

The patient, a newborn girl, the first child of apparently normal parents, was delivered easily with low forceps. There was no difficulty in resuscitation; the baby cried promptly and was taken to the nursery, where she was found to be in good condition and apparently normal. During the first 24 hr. she took small amounts of fluids by mouth and regurgitated only a

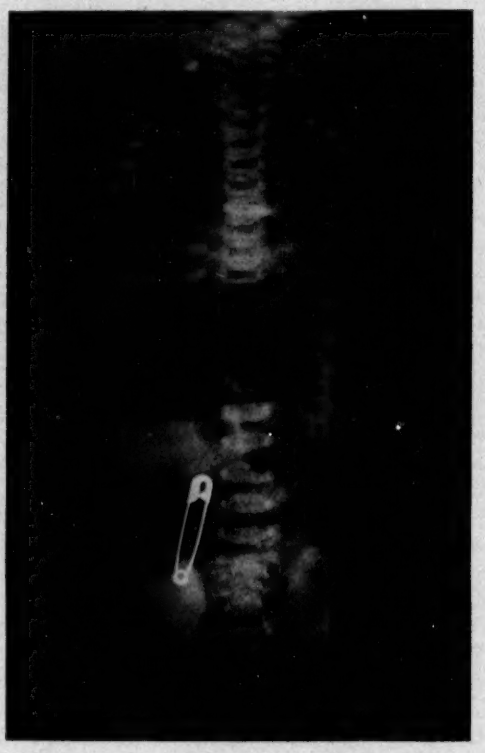

Fig. 1.—Scout roentgenogram showing distended loops of bowel. The distention was thought to be principally in the colon, and this roentgenogram was interpreted as compatible with a low intestinal obstruction.

small amount of the ingested liquids. The nurse on duty stated that regurgitation had been only a little more than that of a normal infant. During the latter part of the first 24-hr. period the infant became fretful and cried intermittently. About 24 hr. after delivery abdominal distention was noted, and no meconium had been passed. Physical examination at that time revealed a slightly dehydrated, crying infant who had generalized abdominal distention. Two dilated coils of bowel could be seen through the abdominal wall. No abdominal masses were felt; no visible peristalsis was seen, and no peristaltic sounds were heard. A rectal examination revealed the anus to be patent, but the examining physician felt what he thought was a

2. Greig, D. M.: Congenital Microcolon, Edinburgh M. J. **32**:175 (April) 1925.

diaphragm obstructing the lumen approximately 5 cm. above the external sphincter. There was a small amount of whitish, caseouslike material and no meconium on the examining finger. An enema was attempted and returned only a small amount of thick, whitish, mucoid-appearing material. A small soft-rubber catheter passed into the rectum met an obstruction about 5 cm. above the anal opening. A scout roentgenogram of the abdomen showed distended loops of bowel compatible with a low intestinal obstruction (Fig. 1). A roentgenogram (Fig. 2) of the abdomen, taken with the baby in the inverted, or head-down, position (Wangensteen maneuver), showed a distended loop of what was erroneously interpreted as large bowel which appeared to follow the course of the colon, terminating in the pelvis. This led to the conclusion that the

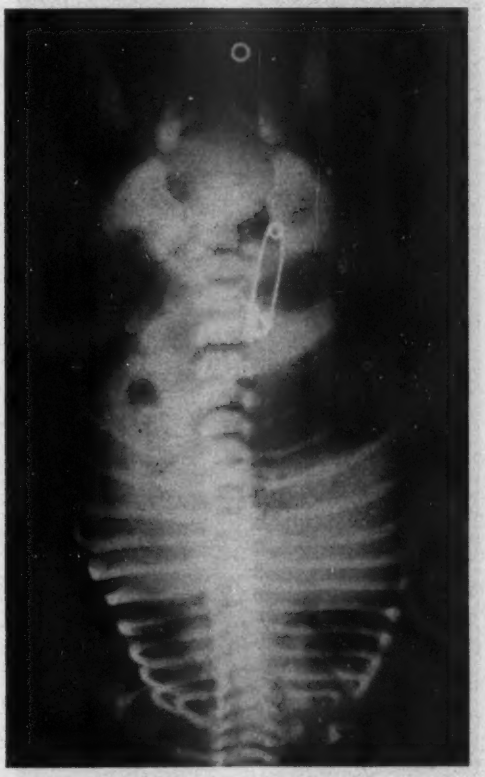

Fig. 2.—Roentgenogram of the abdomen taken with the baby in the inverted, or head-down, position, showing what was erroneously interpreted as large bowel which appeared to follow the course of the colon, terminating just below the pelvic brim. The bowel is distinctly outlined by the gas shadow.

colon was patent, and it was felt that the end of the gas shadow represented the proximal point of obstruction of the colon. A barium enema was unsatisfactory because the barium did not remain in the rectum and would not pass into the sigmoid. The roentgenogram taken with the enema tube in place (Fig. 3), however, did demonstrate the distal point of obstruction. The preoperative impression was that the infant had atresia of a segment of the rectum or at the rectosigmoid junction. The distance between a metallic marker taped over the anal opening and the air column in the colon as seen in a roentgenogram taken with the patient in the Wangensteen position (Fig. 4) showed the height of the obstruction. The area of atresia was

calculated to be short (representing the distance from the tip of the enema tube to the superior limit of the air column in the "colon" with fluoroscopy done with the patient in Wangensteen's inverted position), and it was felt that if the diagnosis proved to be correct, resection of the obliterated segment and restoration of continuity of the colon by an end-to-end anastomosis should be technically feasible.

During the night the infant was given fluids subcutaneously in sufficient amounts and of a composition designed to restore her fluid and electrolyte balance. She was taken to surgery the following morning, approximately 36 hr. after birth. The pertinent operative findings were

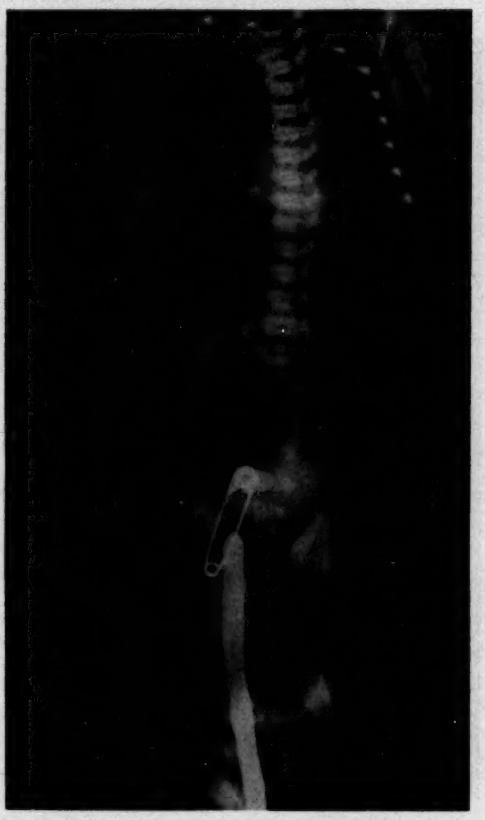

Fig. 3.—Roentgenogram taken with the enema tube in place, demonstrating patency of the anus and rectum. The tube could be passed no farther than shown, and barium would not enter the sigmoid. This established the distal limit of the area of obstruction.

the following (Fig. 5): The stomach was moderately distended. The proximal small bowel was enormously dilated, and at the point of maximum dilatation it was perhaps eight to 10 times the normal caliber. There was a one-turn volvulus in the midileum, and here the distention was most marked. The segment participating in the volvulus was faintly dusky in appearance, but its blood supply did not appear to be significantly compromised. The muscular coats of the dilated small bowel appeared to be definitely hypertrophied, particularly in the distal ileum. As the ileocecal valve was approached, the distention progressively diminished, and the proximal portion of the lower third of the small bowel was almost filled with a semisolid

greenish material. The last foot or so of small bowel was markedly contracted and contained numerous small hard balls of inspissated meconium. These meconium plugs were about the size and shape of green peas. This terminal constricted segment did not exhibit the muscular hypertrophy seen at a slightly higher level. The diminutive ileocecal valve grossly did not appear to be patent. The cecum, and the ascending, transverse, descending, and sigmoid segments of the colon were contracted to an astonishing degree, making ready recognition of the large bowel difficult. This marked constriction was uniform throughout the visible portion of the colon. The mesentery was complete and did not appear unusual except for a proportionate striking decrease in size. The size of the colon was scarely more than one-half that of an ordinary lead pencil. The diameter was estimated to be about 4 mm. The pipe-stem colon appeared to be

Fig. 4.—Roentgenogram taken with the infant in Wangensteen's inverted position, showing the distance between the air column and a metallic marker taped over the anal opening. Comparison with the roentgenogram taken with the enema tube in place appeared to demonstrate a very short area of atresia between the most distal margin of the air column and the tip of the enema tube. Fluoroscopy with the infant in the inverted position with the enema tube in place was thought to confirm that impression.

little more than a fibrous cord, but the external architecture was normal on gross inspection, and on palpation it was not fibrous in consistency. The developmental failure in the colon extended from the tip of the cecum to the proximal rectum, where partial dilatation was observed. The terminal few centimeters of the rectum below the peritoneal reflection was normal. The volvulus was readily reduced. Normal color promptly returned to the involved segment of ileum. A terminal ileostomy was performed a few inches proximal to the ileocecal valve. The infant did not do well after surgery. She remained distended even though con-

siderable inspissated meconium and some gas were passed via the ileostomy opening. Cyanosis, which was present upon termination of the surgical procedure, persisted. In spite of parenteral administration of fluids, continuous administration of oxygen, and numerous attempts at intratracheal suction, she died eight hours after operation.

In addition to the findings described at operation, postmortem examination showed the cause of death to be total right pulmonary atelectasis. The minute colon was found to be patent throughout its entire length in that it was possible to pass a fine probe from cecum to rectum. There was, however, no visible lumen, for the tiny lumen was entirely filled, the mucous lining having secreted its succus entericus, but no meconium was present. The rectum and anus were entirely normal in all respects. No other anomalies were present. Microscopically all coats of the bowel were seen to be present, and these bore a normal proportion to each other; the essential pathological change consisted of a striking diminution in size of all components of the involved large bowel, without other evidence of abnormality. It is perhaps worth while to note that the pancreas was grossly and microscopically normal.

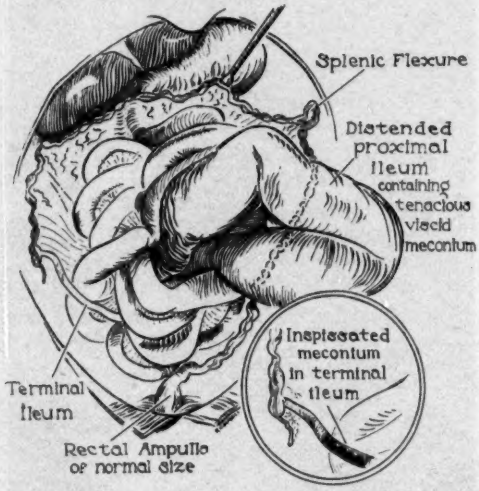
Splenic Flexure
Distended proximal ileum containing tenacious viscid meconium
Inspissated meconium in terminal ileum
Terminal Ileum
Rectal Ampulla of normal size

Fig. 5.—Significant findings at operation. The artist has mislabeled the drawing in that it was the proximal portion of the distal ileum which contained tenacious viscous meconium. The contents of the tremendously dilated proximal ileum consisted chiefly of gas.

COMMENT

Incidence.—According to Webb and Wangensteen,[3] who made a thorough review of the literature, congenital occlusion of the intestine, exclusive of the pylorus, the rectum, and the anal canal, occurs in about 1 of 20,000 infants. Of these intestinal occlusions, congenital stenosis or atresia of the colon is the least common. Consequently, descriptions of the characteristics of these anomalies in the colon have not been given the emphasis that has been given to the occlusions of the small bowel, pylorus, and anus. In many of the standard textbooks of pathology, pediatrics, and surgery scant mention is made of congenital occlusion of the colon. The duodenum is the most frequent site of these lesions; they occur second most frequently in the ileum.

3. Webb, C. H., and Wangensteen, O. H.: Congenital Intestinal Atresia, Am. J. Dis. Child. **41**:262 (Feb.) 1931.

The earliest report of a case of microcolon seems to have been by Osiander,[4] in 1797. In 1903 Clogg,[5] in a review of 181 collected cases of intestinal atresia, found occlusion of the colon in eight cases. Also in 1903 Kuliga [6] described 23 occlusions of the colon in reports of 189 congenital obstructions of the bowel. In 1905, of Kreuter's [7] series of 194 congenital intestinal malformations, 33 showed lesions in the colon. In 1912 Spriggs [8] reviewed reports of 398 congenital occlusions of the intestinal tract, and of these, 20 were in the colon. In 1922 Davis and Poytner [9] reported 39 cases of atresia of the colon among 392 occlusions of the gastrointestinal tract. Greig [2] stated that probably about 5% of all cases of stenosis of the intestinal tract occur in the large bowel. In most of these summaries, however, a clear distinction is not made among microcolon, segmental stenosis, and atresia of the colon. In fact, most of the articles deal principally with malformations of the small bowel, in which congenital narrowings occur more commonly. Also, these reports generally include all degrees of stenosis and atresia and are not limited to cases showing stenosis of the entire colon save the rectum and anus. Greig's [2] paper is an exception. In his splendid article that author has clearly defined congenital microcolon and provided an excellent discussion of the literature to 1924. In 1937 Ewing and Cooke [10] stated that "the incidence of congenital microcolon would appear to be about 1 in 500,000 cases." Gipson, Cross, and Morgan,[11] in 1936 reported two cases of stenosis of the entire colon and commented that in a search of the literature they had been able to find only two authentic cases of similar type. In view of the somewhat loose manner in which the terms atresia, stenosis, and microcolon have been used interchangeably, we believe, as does Greig,[2] that many cases of occlusions of the colon have been inaccurately designated. Because many of the anatomic descriptions in the reported cases have been incomplete, frequently not stating whether or not the stenosed bowel had a lumen and an intact mesentery, we are unable to give an accurate figure for the number of cases identical with our own that have been previously reported. We have found, however, 17 cases [12] in which the findings appear to bear a strong resemblance to the pathological features presented by the case described in this report.

4. Osiander, cited by Greig.[2]

5. Clogg, H. S.: Congenital Intestinal Atresia, Lancet **2**:1770, 1904.

6. Kuliga, P.: Zur Genese der congenitalen Dünndarmstenosen und Atresien, Beitr. path. Anat. **33**:481, 1903; cited by Heckel, N. J., and Apfelbach, C. W.: Congenital Atresia of the Colon, Am. J. Dis. Child. **34**:1050 (Dec.) 1927.

7. Kreuter, E.: Die angeborenen Verschliessungen und Verengerungen des Darmkanals im Lichte der Entwicklungsgeschichte, Deutsche Ztschr. Chir. **79**:1, 1905; cited by Heckel, N. J., and Apfelbach, C. W.: Congenital Atresia of the Colon, Am. J. Dis. Child. **34**:1050 (Dec.) 1927.

8. Spriggs, N. I.: Congenital Occlusion of the Gastro-Intestinal Tract, Guy's Hosp. Rep. **66**:143, 1912.

9. Davis, D. L., and Poytner, C. W. M.: Congenital Occlusions of the Intestines, with Report of a Case of Multiple Atresia of the Jejunum, Surg., Gynec. & Obst. **34**:35 (Jan.) 1922.

10. Ewing, J. B., and Cooke, W.: Two Cases of Congenital Microcolon, Brit. J. Surg. **25**:506 (Jan.) 1938.

11. Gipson, A. C.; Cross, E. H., and Morgan, J. O.: Congenital Stenosis of the Entire Colon, Am. J. Dis. Child. **54**:1320 (Dec.) 1937.

12. Heckel, N. J., and Apfelbach, C. W.: Congenital Atresia of the Colon, Am. J. Dis. Child. **34**:1050 (Dec.) 1927. Cole, W. H.: Congenital Malformation of the Intestinal Tract and Bile Ducts in Infancy and in Childhood, Arch. Surg. **23**:820 (Nov.) 1931. Abdala, J. R.; Itoiz, O. A.; Pellerano, J. C., and Schere, S.: Microcolon congénito, Arch, argent, pediat. **9**:33 (Jan.) 1938. Schroeder, E.: Congenital Microcolon, Hospitalstid. **80**:897 (Aug.) 1937.

(Footnote continued on next page)

Etiology.—It is beyond the scope of this paper to enter into a detailed discussion of the embryology and etiological factors in congenital occlusions of the intestinal tract. The normal embryological development of the gastrointestinal tract is well covered in standard texts on the subject. In his classic treatise on congenital microcolon Greig discusses at some length the following theories of etiology: (1) absence of vis a tergo; (2) occlusion of bowel lumen; (3) meconium ileus; (4) congenital want of patency of the ileocecal valve; (5) insufficient blood supply, and (6) defective nerve mechanism. He concluded that the phenomenon of congenital microcolon could best be explained on the basis of defective nerve mechanism, viewing the pathological features as the result of a physiological aberration rather than an anatomical defect. Greig concluded that the fault was an achalasia—a want of relaxation—due to a defect in the autonomic nervous system. More recently, Webb and Wangensteen have presented a thorough consideration of the various theories as to the cause of intestinal occlusions. Probably the most important of these hypotheses are (1) the Bland-Sutton [13] theory, which holds that intestinal occlusions occur at the site of embryological events; (2) the vascular defects theory of Jaboulay [14] and Wyss,[15] which suggests that many intestinal occlusions result from defects in vascular supply of the intestine; (3) the theory of Tandler [16] and Krueter,[7] who found that the original lumen of the intestinal canal of most vertebrates is lost in the early part of embryonic life by epithelial proliferation, but is later reestablished, and who assume that in congenital intestinal occlusions recanalization has not occurred; (4) the theory that proposes intrauterine inflammatory reactions as a possible cause of these anomalies, and (5) the theory that defective internal rotation might be the basis for these defects.

Although the theory of a defective nerve mechanism impresses us as the most logical explanation for congenital microcolon, it is possible that no one cause accounts for all cases of congenital intestinal occlusion of this type.

Diagnosis.—The clinical recognition of congenital intestinal occlusion is not difficult if the condition is kept in mind. The infant usually appears normal and takes his feedings well for the first few hours or even the first day. He then becomes fretful, and in nearly all cases, regurgitation or vomiting begins within 24 hr. Vomiting is the outstanding early symptom, and its onset is usually related to the location of the obstruction; it occurs early, within a few hours, in high obstructions and late, about the second day, in low obstructions. The vomiting may be fecal and projectile or it may be regurgitation only slightly in excess of normal. There is absence of meconium (Farber's sign), although the infant may pass small amounts of greyish-white to light-green mucus, which is in sharp contrast to the tarry appearance of normal meconium. No stools, as such, are passed by patients with microcolon, and green mucus is not evacuated. The absence of normal bile-stained

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Sims, G. K., and Meyers, H. L.: Report of a Case of Congenital Malformation and Arrested Development of the Colon, Am. J. Obst. & Gynec. **12**:887 (Dec.) 1926. Cafritz, E. A., and Greenberg, M.: Congenital Microcolon: A Case Report, Ann. Surg. **129**:285 (Feb.) 1949. Ewing and Cooke.[10] Gipson, Cross, and Morgan.[11]

13. Sutton, J. B.: Imperforate Ileum, Am. J. M. Sc. **98**:457, 1889.

14. Jaboulay, M.: Chirurgie des centres nerveux, des viscères et des membres, Paris, O. Doin, 1902, Vol. 2, p. 43, cited by Spriggs.[8]

15. Wyss, M. O.: Über congenitale Duodenal-Atresien, Beitr. klin. Chir. **26**:631, 1900.

16. Tandler, J.: Zur Entwicklungsgeschichte des menschlichen Duodenum in frühen Embryonalstadien, Morphol. Jahrb. **29**:187, 1902; cited by Webb and Wangensteen.[3]

meconium when there is associated vomiting is presumptive evidence of intestinal obstruction. It has been stressed by Webb and Wangensteen [8] that bile-stained meconium is usually present in obstructions above the terminal common bile duct and that the spontaneous evacuation of stools or the effectual return of meconium and gas does not rule out the presence of intestinal obstruction. Ineffectual enemas are significant of the presence of a low obstruction, however.

Abdominal distention is a frequent and prominent but usually a comparatively late sign. It varies with the level of the obstruction and may be marked in low obstruction. Visible peristalsis is a pathognomonic sign of obstruction, partial or complete, but is usually seen only in subacute or chronic types of obstruction and is very rarely observed in congenital occlusions. As a result of the loss of fluids and the lack of absorption, dehydration is frequently evidenced by oliguria or anuria, poor tissue turgor, depression of the fontanels, loss of weight, and fever. Jaundice may be a late sign.

If these infants are carefully observed during the first 24 to 48 hr., the clinical findings are usually sufficient to make a diagnosis of intestinal obstruction. However, roentgen examination is of great help in confirming the clinical diagnosis and of considerable value in locating the site of the obstruction. A simple roentgenogram of the abdomen taken in the upright position will show distended loops of bowel with fluid levels. The distended loops of bowel will indicate whether the obstruction is high or low. It must be remembered, however, that a paralytic ileus also gives rise to a distended intestine. Webb and Wangensteen [8] have previously noted that gas may be constantly observed in the small intestine of infants. They state that "its presence in the infant with suspected obstruction of the bowel is not of the same significance as it is in adults and older children." Roentgen examination, however, does indicate that abnormal intestinal distention is present, and in the presence of loud intestinal borborygmi, in contrast to the relative silent abdomen of paralytic ileus, it is of significant aid in confirming the diagnosis of intestinal obstruction. If the obstruction is thought to be low in the colon, additional information concerning the level of the occlusion may be obtained by taking roentgenograms of the infant with its head down, as described by Wangensteen and Rice,[17] in order to determine the position of the blind rectal pouch.

The administration of barium to these infants is not without danger and is condemned by many authorities. If for any reason it is given, certainly a thin mixture should be used, and as much of the barium as possible should be removed by aspiration. In our opinion a study of the distended loops of bowels on the plain roentgenogram reveals adequate information and the use of barium by mouth is neither indicated nor advisable. According to Ladd and Gross,[18] a barium enema to determine the patency of the colon should never be employed. It adds to the great discomfort and distress of these already distended infants, and even if an obstruction in the colon were demonstrated, it would not alter the operative exposure in any way.

Differential Diagnosis.—The striking similarity between the symptomatology, roentgenographic picture, clinical course, and operative findings in infants with

17. Wangensteen, O. H., and Rice, C. O.: Imperforate Anus: Method of Determining Surgical Approach, Ann. Surg. **92**:77 (July) 1930.

18. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1947.

congenital microcolon and in those with meconium ileus requires comment. Indeed, they are clinically indistinguishable, and, further, we know of no means whereby a positive differentiation can be made even at operation. This is most disturbing in view of the fact that the surgical therapy required in the two conditions differs so widely. Meconium ileus, first described by Landsteiner [19] in 1905, is a rare disorder characterized by a clinical picture identical with that described for congenital microcolon and with operative findings duplicating in almost every detail those exhibited in the case reported above. The important difference of the two conditions appears to lie in the fact that meconium ileus is invariably associated with fibrocystic disease of the pancreas in a patient whose colon, though contracted, is normal and capable of dilatation, while in congenital microcolon, the large bowel is truly underdeveloped and the pancreas is normal. We have never encountered a case of meconium ileus and therefore cannot state from firsthand knowledge how the two conditions can be distinguished from each other at the time of operation. From a review of the literature, however, one may assume that the really startling reduction in caliber of the large bowel (to 3 to 4 mm. in our case, with no grossly demonstrable lumen) seen in congenital microcolon would not be encountered in meconium ileus. It is inconceivable that the intestinal contents, regardless of their consistency, could ever successfully pass through the minute lumen of a congenital microcolon showing the usual high degree of stenosis.

As is true of congenital microcolon, meconium ileus is a rare lesion, only 26 cases having been reported through September, 1948. These have been reviewed in an excellent article by Hiatt and Wilson.[20] These authors have stressed a reduction of the tryptic activity of the duodenal secretions from a normal of approximately 100 units per cubic centimeter to something on the order of two to four units per cubic centimeter. Time and the patient's condition permitting, it would appear that this would be a most important differential diagnostic test to carry out in any infant in whom the existence of either congenital microcolon or meconium ileus is suspected preoperatively. Hiatt and Wilson have advised a conservative type of surgical procedure in the latter disorder, consisting in ileotomy, the most thorough possible removal of the hardened, inspissated meconium, the instillation of 30 to 50 cc. of 5% pancreatin solution in the distal ileum, and closure of the bowel. Five of eight infants so treated survived. A careful program of postoperative medical management doubtless contributed much to these most excellent results, and those interested in meconium ileus are urged to consult Hiatt and Wilson's original article.

Treatment.—The treatment of patients with congenital occlusion of the intestine is surgical, and although the mortality rate is still quite high, surgical intervention should be undertaken in every case, no matter how critical the condition of the baby may be. Every effort should be made to bring these infants to surgery as soon as they are properly prepared.

Babies with intestinal obstruction are usually in a state of moderate dehydration, and surgical intervention should not be undertaken until that condition is corrected. Parenteral administration of fluid is essential, and the total fluid intake should be

19. Landsteiner, cited by Hiatt, R. B., and Wilson, P. F.: Celiac Syndrome: VII. The Therapy of Meconium Ileus: Report of 8 Cases with a Review of the Literature, Surg., Gynec. & Obst. **87**:317 (Sept.) 1948.

20. Hiatt, R. B., and Wilson, P. F.: Celiac Syndrome: VII. The Therapy of Meconium Ileus: Report of 8 Cases with a Review of the Literature, Surg., Gynec. & Obst. **87**:317 (Sept.) 1948.

50 to 75 cc. per pound (0.5 kg.) of body weight in 24 hr. One may give isotonic saline solutions in the amount of 10 to 15 cc. per pound of body weight in 24 hr. and the rest of the total intake in 5 to10% dextrose solutions. Addition of potassium to the fluid given parenterally may occasionally be necessary. Small blood transfusions (50 to 75 cc.) are given as indicated, especially if there has been any suggestion of hemorrhagic disease of the newborn. Prior to operation a No. 8 to 10 soft-rubber nasogastric tube is passed, and all fluid and gas is removed from the stomach by suction with a syringe. The catheter is left in place during the operation, and postoperatively it is attached to a Wangensteen suction apparatus.

During the operation, the infant should be kept warm by a hot-water bottle placed under the back, and the arms and legs should be wrapped with sheet wadding to conserve body heat. Both local analgesia and open drop ether have been recommended for anesthesia in these cases, but we believe that ether gives better relaxation and exposure and consider it the anesthetic of choice. We agree with Ladd and Gross that "a 3-4 inch right rectus muscle splitting or retracting incision, with its midpoint opposite the umbilicus, will give adequate exposure to any part of the intestinal tract." [18]

Whenever it is at all possible, the continuity of the bowel should be restored. A side-to-side anastomosis is customarily used in these infants because the suture of such small intestines usually cannot be completed by the end-to-end type. According to Ladd and Gross,[18] this should be done without the application of clamps to the tiny collapsed distal bowel, but a small intestinal clamp may be used on the upper segment to prevent soiling. They further state that the use of the aseptic types of anastomosis is not practical with such small intestines, and we do not feel that that technique is necessary. Only a very fine silk suture should be used, and a single running suture by the Connell method will usually give a satisfactory anastomosis. Since the small size of the distal intestine leads to partial obstruction after the anastomosis has been performed, every effort should be made to distend the distal bowel. This can be done by injecting isotonic sodium chloride solution or small amounts of liquid petrolatum into the lower loop before completing the anastomosis. If, of course, in a case believed to represent congenital microcolon the remotest possibility of meconium ileus is entertained, 5% pancreatin in water should be instilled in lieu of the foregoing solution.

"The treatment of the patient following operation demands a great deal of patience, attention and supportive care." [18] Upon return to the nursery the infant is given 50,000 units of penicillin, followed by 10,000 or more units every three hours. Wangensteen siphon-suction gastric drainage is continued as long as there is any tendency of the patient to vomit. On about the third postoperative day, or when there is evidence that the vomiting has virtually ceased, the catheter and suction apparatus are removed and a routine postpyloric-obstruction regimen of feeding is begun. Parenteral administration of fluids is continued, and blood is given as necessary. Administration of aureomycin orally may also be indicated.

Both Webb and Wangensteen [8] and Ladd and Gross [18] have stressed the fact that ileostomy is contraindicated in congenital intestinal occlusions. The use of an enterostomy in a newly born infant commonly leads to extreme dehydration which cannot be combated, even with vigorous administration of fluids parenterally and blood. All patients treated thus far by enterostomy have died. However, Ladd and Gross [18] mentioned two patients who lived for three and four weeks respectively, and they suggest that it may be of value as a temporary procedure.

We have no proved solution to offer for the successful treatment in cases of congenital microcolon. If an infant with this anomaly survives an ileostomy and within a relatively short time it is found possible to anastomose the terminal ileum to the rectum, we believe that an occasional patient may be salvaged. The dilated and hypertrophied state of a large part of the ileum should make an end-to-end anastomosis between the ileum and the rectum a fairly easy technical undertaking. It may be contended that this would constitute little more than an ileostomy functionally and that it is not likely that the short rectal pouch would adequately prevent the abnormal loss of fluids and electrolytes to which infants with an ileostomy are subject. However, we do not view the possibilities of the procedure with such pessimism. Patients of young age who have had all the colon save the anorectal segment removed for congenital familial polyposis of the colon have been found not to fare poorly from the nutritional standpoint. Since no successfully treated patients with congenital microcolon have been reported in the literature, it appears that the suggested procedure should be worthy of a trial. Better understanding of the problem of fluid and electrolyte balance in infants as a result of the contributions of Gamble, Darrow, and others may make it possible to carry these infants along with an ileostomy until the second stage of the operation can be accomplished. For the present, congenital microcolon must be listed as a condition for which no surgical solution has been found and one whose treatment presents a distinct challenge to those interested in pediatric surgery.

Prognosis.—The outlook for infants with congenital intestinal occlusion is still rather poor, but the prognosis is not nearly so dismal [21] as that prevailing a few years ago. It has been the persistent work of Ladd and Gross, Webb and Wangensteen, Potts,[22] Cole, Miller, Donovan, Duckett, and others interested in this subject that has contributed most to the constantly improving mortality figures. Earlier diagnosis, immediate treatment, including the employment of effective antibiotic or chemotherapeutic agents, intelligent correction of fluid and electrolyte balance while avoiding overhydration, and the utilization of improved surgical and anesthetic techniques have made the prognosis reasonably good for those full-term infants whose only defect consists of a surgically correctable congenital occlusion of the bowel. Despite these heartening advances, however, no successfully treated patient with microcolon has yet been reported.

SUMMARY AND CONCLUSIONS

A case of congenital microcolon has been reported and the literature briefly reviewed. The diagnosis, treatment, and prognosis of congenital intestinal occlusions, with emphasis on congenital microcolon, have been discussed. The similarity of microcolon to meconium ileus is mentioned.

Early diagnosis and prompt, adequate surgical therapy will lead to a gratifying percentage of successes in the management of congenital intestinal occlusions.

The problem of congenital microcolon per se has not been solved. In view of the universal failure by previously tried methods in the treatment of this anomaly, a new procedure is suggested that may offer some hope of success.

21. Bockus, H. L.: Gastro-Enterology, Vol. 2, Philadelphia, W. B. Saunders Company, 1947, p. 391.

22. Potts, W. J.: Congenital Atresia of the Intestine and Colon, Surg., Gynec. & Obst. **85**:14 (July) 1947.

Abstracts from Current Literature

Biochemistry; Bacteriology and Pathology

REEVALUATION OF ETHYL ALCOHOL AS A GERMICIDE. PHILIP B. PRICE, Arch. Surg. **60**:492 (March) 1950.

A new effort was made to settle the old but still controversial question of the germicidal value of ethyl alcohol. In vitro studies, using the quantitative "spoon test" with bacteria in aqueous suspension, have shown that some concentrations of alcohol are important but that others are strongly and rapidly germicidal. It was shown that 10 and 20% solutions by weight have little or no bactericidal effect in 10 min. or less at room temperature; 30, 40, and 50% solutions show progressively greater germicidal power, and 60 to 90% solutions by weight are all strongly and rapidly bactericidal, much of the killing effect apparently taking place during the first few seconds of contact. Absolute alcohol is somewhat less effective. Seventy per cent alcohol by weight is still believed to be the solution of choice for disinfection of the skin.

KAISER, Rochester, N. Y.

Metabolism; Infant Feeding; Milk and Other Foods

THE GLYCEMIC RESPONSE OF THE NEWBORN INFANT TO EPINEPHRINE ADMINISTRATION: A PRELIMINARY REPORT. MURDINA M. DESMOND, JACK R. HILD, and JOSEPH H. GAST, J. Pediat. **37**:341 (Sept.) 1950.

Newborn and premature infants often have low blood glucose levels. It has previously been suggested that this may be due to difficulty in mobilization of available liver glycogen. With this in mind, glycemic response to epinephrine injection was studied in 63 infants. Although most infants showed a definite rise in blood glucose after epinephrine injection, the responses were too variable for this test to be used as a test of liver function. In the early days of infancy the rise and fall of blood glucose is slower than that seen in infants older than 1 week. In the first 24 hr., response to epinephrine given subcutaneously is less than that seen when the injection is intramuscular. After the first 24 hr., the method of injection does not influence the results.

MACDONALD, Pittsburgh.

RELATIONSHIP OF ABILITY TO BREAST FEED AND MATERNAL ATTITUDES TOWARD BREAST FEEDING. NILES RUMELY NEWTON and MICHAEL NEWTON, Pediatrics **5**:869 (May) 1950.

Ninety-one mothers were interviewed shortly after delivery to ascertain their attitudes toward breast feeding. Independent judges divided the attitudes into three categories on the basis of written records of the interview.

Of the mothers who expressed positive attitudes toward breast feeding, 74% had enough milk by the fifth day after delivery to make formula supplementation unnecessary. Only 35% of those who expressed doubtful and 26% of those who expressed negative attitudes toward breast feeding had enough milk to make formula supplementation unnecessary by the fifth day.

Mothers with positive attitudes gave a larger average amount of milk on the fourth day, reported slightly more signs of let-down, and used nipple shields less frequently than the mothers with negative attitudes. Mothers with positive attitudes reported that their babies had less difficulty sucking and less frequently refused the breast, but more frequently refused the bottle, than those mothers with negative attitudes. The course of lactation in the mothers with doubtful attitudes, although on the whole more like that of the negative group, did follow in some ways that of the positive group. The incidence of crying at the breast and biting or chewing the nipple was the same in all three attitude categories.

The implications of this study on the management of breast feeding are discussed.

FROM THE AUTHORS' SUMMARY.

Vitamins; Avitaminoses

ACTION OF VITAMIN H_2 (PARAAMINOBENZOIC ACID) ON THE SMALL BLOOD VESSELS OF THE SKIN AND OF INDUCED EDEMA. P. NICOLAJ, Clin. Pediat. **31**:659 (Dec.) 1949.

Paraaminobenzoic acid when given to children did not change the fragility of the skin capillaries but did cause a quicker absorption of artificially induced edema.

HIGGINS, Boston.

AVITAMINOSIS H. V. TRIPPUTI, Lattante **21**:78 (Feb.) 1950.

Eight infants presented the syndrome of erythema and desquamation of the skin and the occurrence of frequent loose bowel movements. Administration of biotin (vitamin H) led to rapid and permanent relief of the symptoms.

HIGGINS, Boston.

SUITABLE MASSIVE SINGLE DOSE OF VITAMIN D_2 FOR CHILDREN. A. CARNEVALE, Lattante **21**:290 (May) 1950.

A massive single dose of vitamin D_2 (200,000 units) was given to 17 children, of whom some had rickets, some were convalescent from an infectious disease, and some had active tuberculosis. Studies of the blood phosphate, calcium and hemoglobin indicate that this dosage is suitable, especially when supplemented with calcium salts.

HGGINS, Boston.

Hygiene; Growth and Nutrition, Public Health

GROUP SOCIAL SERVICE OR GROUP WORK: ITS TRUE DENOMINATION: EDUCATION OR RESOCIALIZATION IN NUCLEI. BLANCA A. CASSAGNE SERRES, Bol. del Inst. internac. Am. protec. infancia **24**:36 (March) 1950.

The author deems it more correct to say that the child must be formed in a "nucleus" (family, school, social, or other) than in a "group," the word which is usually employed, because "nucleus" implies a homogeneity and common interest which is not implied by "group." She studies the conditions which are necessary for a good education or resocialization in a nucleus to occur.

She considers that "school clubs," recently created in Argentina, as well as the summer camps, may constitute primary organizations in which true democracy can be taught and learned.

FROM THE AUTHOR'S SUMMARY.

NUTRITIONAL AND HEALTH CONDITIONS OF INFANTS IN THE POSTWAR PERIOD. SPIESS, Monatsschr. f. Kinderh. **97**:242 (Sept.) 1949.

Examination of 1,000 infants from birth until 1 yr. of age in an infant welfare station in Goettingen, Germany, during 1946-1947 showed the following results: Growth was normal. Weight gains fell below normal during the second six months of life. Breast feeding was markedly reduced as compared with prewar years. Quality and caloric values for breast milk were found to be deteriorated because of decrease in albumin and fat. Mothers with low albumin content of their milk were found to have low serum albumin, probably because of poor maternal nutrition. Commercially obtainable cow's milk was also found to be low in fat and albumin, and feeding of two parts cow's milk and one part water at 6 weeks and whole cow's milk at 5 mo. is advised. Florid rickets was noted in 50% of all infants seen. Infant mortality during the first year of life was 7% as compared with 3.8% in 1938.

HARTENSTEIN, Chicago.

Prematurity and Congenital Deformities

RENTROLENTAL FIBROPLASIA. RALPH O. RYCHENER, Illinois M. J. **96**:299 (Nov.) 1949.

In this discussion Rychener points out that rentrolental fibroplasia is one of the diseases peculiar to extremely premature infants. It dooms the infant to blindness and frequently to cerebral dysplasia. In the typical case an opaque, vascularized membrane lies against the posterior surface of the lens. Recent investigation seems to indicate that the membranes arise from the

retina behind the ciliary body, are present before delivery, and tend to increase in size postnatally. Clinical observations have clarified the nature and origin of the lesion but have added nothing as to the cause of the disease. Treatment with radium, x-ray, diathermy, and surgery have been entirely without avail. Prevention is the only hope for its eradication. Two of the author's cases are reported.

BARBOUR, Peoria, Ill.

OXYCEPHALY. M. BODIAN, J. A. M. A. **143**:15 (May 6) 1950.

Oxycephaly consists of a group of congenital deformities resulting from premature closure of the bony vault of the skull. The outstanding feature is a tower-shaped head. Developmental anomalies of other parts of the body are frequently associated. Because of the numerous ocular observations, the ophthalmologist sees many of these patients.

Bodian reports a case of typical oxycephaly with optic-nerve atrophy in a young Negro boy. The role of injury to the eyes of oxycephalic persons is strikingly demonstrated in this case.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

RECURRENT ANENCEPHALY. N. FERRERLICHT, J. A. M. A. **143**:23 (May 6) 1950.

In spite of statistical evidence to the contrary, there persists general acceptance of the belief that congenital abnormalities are unlikely to recur. According to Murphy, however, a mother of a defective child is 25 times as likely to produce another defective offspring as is a mother in the general population. Further, Murphy showed that there is nearly one chance in two that a subsequent malformed child will exhibit the same defect as that shown by its earlier-born sibling.

Ferrerlicht reports a case of recurrent anencephaly in a primigravida aged 21 at the first delivery and 23 at the second delivery. The incidence of recurring anencephaly is high. Female anencephalics predominate. Generally the bodies of anencephalics are well-formed. In this condition the length of gestation is abnormal, and hydramnios is a common complication.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

SPECIFIC DEVELOPMENTAL INHIBITIONS PRODUCED IN AMPHIBIAN EMBRYOS BY A NITROGEN MUSTARD COMPOUND. ROY GILLETTE and DIEDRICH BODENSTEN, J. Exper. Zool. **103**:1 (Oct.) 1946.

Embryos of Triturus torosus (stage 36) were exposed 45 min. to a 0.001% solution of a nitrogen mustard compound (methyl-bis-[chlorethyl] amine hydrochloride). This chemical agent affected mitotic processes within proliferating cells without retarding histologic differentiation.

In those regions of the neural tube and eye where histologic differentiation occurs in nonmitotic cells, differentiation proceeded at the same pace as in control embryos. However, in the germinal regions of these organs (ependymal layer of the neural tube and the rim of the iris in the eye) mitosis was inhibited for about 10 days, whereas the cells continued to grow. Mitosis, when it finally occurred, resulted in disruption of the cells and the destruction of the germinal regions.

A large number of mitotic cells did not exhibit this characteristic reaction but broke down completely within five days of exposure. Such cells were concluded to be still undergoing the cleavage type of mitosis. The characteristic reaction to exposure of the germinal cells showed that they were already physiologically set aside from the cleavage type of mitotic cell, although at that early stage they could be identified only by position.

Fully developed organs suffered less destruction than those which were in a more primitive state. For example, cranial cartilages and sensory ganglia were little affected, whereas trunk cartilages and sensory ganglia were completely suppressed.

The selective action of the agent on mitosis, but not on differentiation, was demonstrated by the reaction of gut and epidermal cells when these two processes occur in the same cell. Although mitosis was stopped, the cells continued to grow and became abnormally large. However, in these enlarged cells the characteristic histologic differentiation occurred at the same time as in the smaller cells of the unexposed animals.

The nitrogen mustard compound not only revealed centers of proliferation but arrested proliferating organs in various stages of development. Organs of various sizes, depending on their developmental condition at the time of exposure, could thus be produced.

REID, New Brunswick, N. J. [ARCH. NEUROL. & PSYCHIAT.].

STUDIES ON PREMATURITIY: II. INFLUENCE OF FETAL MATURITY ON FATALITY RATE. MORRIS STEINER and WILLIAM POMERANCE, Pediatrics **6**:872 (Dec.) 1950.

The fatality rate among 791 live-born premature infants delivered at the Jewish Hospital of Brooklyn during the five-year period from 1941 to 1945 was investigated. The data were analyzed to determine the significance of fetal maturity and of magnitude of birth weight as factors influencing survival.

It was found that for a given weight group, the fatality rate varied inversely with the length of the gestation period. In other words, the outlook for the infant improved in proportion to the degree of its maturity. This was especially striking in the case of infants weighing less than 1,500 gm., a result which served to emphasize the importance of length of gestation period, as well as birth weight, in predicting the chance of survival.

Premature infants born of multiple births had a lower over-all fatality rate than those born of single births. This was directly attributable to the greater maturity of babies born of multiple births.

FROM THE AUTHORS' SUMMARY.

DIGESTION OF PROTEIN BY PREMATURE INFANTS AS INDICATED BY NITROGEN ABSORPTION FROM WHOLE VS. HYDROLYZED PROTEIN. MYRON S. FEINSTEIN and CLEMENT A. SMITH, Pediatrics **7**:19 (Jan.) 1951.

Absorption of nitrogen from cow's-milk mixtures supplemented with equal amounts of nitrogen as casein and casein hydrolysates was determined in 20 metabolic periods on five premature infants. The supplemental protein or hydrolysate furnished from 33.3 to 46.2% of the nitrogen intake, and total nitrogen fed was equivalent to 4.22 to 8.49 gm. of protein per kilogram of body weight. With either supplement, from 86 to 94% of the dietary nitrogen was absorbed, and neither resulted in consistently superior nitrogen absorption. Weight gains were not consistently better during either type of supplemental feeding. The evidence of equally satisfactory nitrogen absorption and weight gain would substantiate the prevailing belief that protein digestion is not impaired after premature birth.

FROM THE AUTHORS' SUMMARY.

MEAT IN THE DIET OF PREMATURE INFANT. THOMAS R. C. SISSON, ANNE F. EMMEL, and LLOYD J. FILER JR., Pediatrics **7**:89 (Jan.) 1951.

Meat protein is as well retained and utilized as milk protein by the premature infant and therefore is as safe and efficient a source of protein as milk. The fat absorption of the premature infant is not significantly altered when the milk fat in the diet is partly or wholly replaced by meat fat or meat fat and olive oil.

Strained meats do not contain a sufficient quantity of calcium and phosphorus to maintain an adequate intake of these minerals for the premature infant without further supplementation from other courses, such as milk or pure mineral supplements.

Strained meats are an excellent and readily available source of iron for premature infants. The iron of meat is absorbed by them, but how well it is stored and utilized by them requires further investigation.

FROM THE AUTHORS' SUMMARY.

HARELIP AND CLEFT PALATE REPAIR. E. C. PADGETT, Plast. & Reconstruct. Surg. **2**:374 (July) 1947.

In this paper the author reports the cases he presented at the 1946 meeting of the American Society of Plastic and Reconstructive Surgery. Included in the series are six patients with single harelip, ranging in age from 2 mo. to 16 yr.; five patients with double harelip and palate defect: two patients with double harelip and palate defect, and two patients with double

harelip without palate defect. Padgett chose 18 mo. as the routine age for operation; he used the Diffenbach-von Langenback method, which is briefly outlined. The procedures for reconstruction and repair are also considered. Excellent photographs of the lesions before and after operation are included.

SELTZER, Philadelphia [ARCH. OTOLARYNG.].

PRIMARY CLOSURE OF HARELIP. V. P. BLAIR and R. R. ROBINSON, Surg., Gynec. & Obst. **86**:502 (April) 1948.

In this article the authors deal editorially with the subject of cleft lip. They point out that refreshening and uniting of the border of a cleft does not usually give satisfactory results. The reason for the operation is that it provides free breathing and assures that the lip will be symmetric. Deformity is caused partly by some reduction in the amount of lip tissue in all instances but chiefly by tissue displacement. The first step is to mark out a pattern for incisions that will allow adjustment of the soft tissues without much tension. There is no single rule for doing this, since conditions are seldom exactly alike. An operation done early, during the first two days of an infant's life, is simple, and at two weeks thereafter the infant will present a nearly normal appearance, which is gratifying to the parents. Secondary operation may be needed some time during the first two years of life. If the primary operation is delayed until later childhood, there may then be a greater deformity that will require more extensive operation for correction, with a greater degree of undermining and removal of segments of both skin and cartilage to raise the displaced alae to the proper position. If the defect is not corrected earlier, at adolescence deflection of the nose may necessitate an extensive plastic operation. Many methods have been used for correcting cleft lip and palate, but the authors suggest means for closing complete double cleft lip and palate in two steps: 1. The premaxilla should be corrected by the Rose or Mirault method to give good occlusion of incisors and suitable contour of face. 2. The shortening of the nose resulting from the push-back of the premaxilla in closing the hard palate should be corrected by raising the superficial lip flaps and separating, at the same time, the short columella from the septum. Detailed directions are given for this operation, with the reminder that if the operation is not carefully performed from the beginning, the final result will be unsuccessful; but if it is properly performed, the outcome should be satisfactory.

SELTZER, Philadelphia [ARCH. OTOLARYNG.].

RETROLENTAL FIBROPLASIA: A CAUSE OF BLINDNESS IN PREMATURE INFANTS. BEN EPSTEIN, South African M. J. **24**:275 (April 15) 1950.

Epstein gives in this paper a very brief review of the current literature on retrolental fibroplasia.

McGUIGAN, Evanston, Ill.

USE OF PROTEIN HYDROLYSATE IN THE TREATMENT OF THE IMMATURE INFANT. L. LANDUCCI, **21**:297 (May) 1950.

Clinical studies on 20 premature infants, to whom 1.5 to 5 gm. of the amino acids from hydrolyzed protein were fed daily, revealed excellent results.

HIGGINS, Boston.

Newborn

PROTHROMBIN IN THE NEWBORN INFANT: V. FURTHER OBSERVATIONS ON THE NATURE OF PROTHROMBIN IN THE NEWBORN INFANT: COMPARATIVE EFFECT OF STORAGE ON PROTHROMBIN OF THE NEWBORN INFANT AND NORMAL ADULT. SIMON KOVE and CHARLES BENTON, J. Pediat. **37**:78 (July) 1950.

The authors present evidence that the plasma prothrombin of the newborn infant and that of the normal adult are qualitatively and physiologically similar. They suggest that other accelerator and inhibiting factors in the clotting mechanisms are also similar for the infant and the adult. Fresh plasma is a ready source of prothrombin. Plasma stored longer than one week is a poor source of prothrombin.

MACDONALD, Pittsburgh.

PROTHROMBIN IN THE NEWBORN INFANT: VI. EFFECT OF SULFADIAZINE ON PROTHROMBIN OF THE NEWBORN INFANT. SIMON KOVE and CHARLES BENTON, J. Pediat. **37**:90 (July) 1950.

Sulfadiazine, 1 grain (0.06 gm.) per pound (0.5 kg.) of body weight per 24 hr., given for three days to newborn infants had no effect on prothrombin. The prothrombin concentration did not fall but rose, as was expected in these infants who normally have initial hypoprothrombinemic levels. Therefore, administration of vitamin K is good as routine therapy at birth but is not necessarily indicated as an adjunct to sulfonamide therapy given over a short period to a newborn.

MACDONALD, Pittsburgh.

CONGENITAL THROMBOCYTOPENIC PURPURA OF THE NEWBORN INFANT. HARRY R. LITCHFIELD and S. DAVID STERNBERG, J. Pediat. **37**:94 (July) 1950.

A woman who bruised easily became pregnant, and during pregnancy this bruising tendency disappeared. Her male infant exhibited purpura one-and-one-half hours after birth; he had thrombopenia, positive tourniquet reaction, and prolonged clot-retraction time. There was no splenomegaly. He recovered spontaneously and quickly within a few days.

MACDONALD, Pittsburgh.

CHOICE OF ROOMING-IN OR NEWBORN NURSERY: ANALYSIS OF DATA FROM PRENATAL SCREENING INTERVIEWS OF 1251 MOTHERS, RELATING TO THEIR CHOICE OF HOSPITAL ACCOMMODATION FOR THEIR INFANTS IN A ROOMING-IN UNIT OR IN THE NEWBORN NURSERY. ETHELYN H. KLATSKIN, ANTON N. LETHIN, and EDITH B. JACKSON, Pediatrics **6**:878 (Dec.) 1950.

From July 1, 1947, to July 1, 1949, 1,251 mothers attending the obstetric clinic of the university service of the Grace-New Haven Community Hospital were "screened" through interview to determine their preference in hospital accommodation and to obtain basic identification data. Patients were grouped according to preference for rooming-in, preference for nursery, and undecided. The significance of the relation between accommodation preference and patient's feeding preference, parity, age, education, descent, religion, and race, and occupation of patient's husband were then statistically determined. It was found that inclusion of data of the undecided group with that of the nursery group did not alter the statistical significance of any of the obtained relation, and consequently only the rooming-in and nursery groups will be contrasted in the following summary:

1. A highly significant relation was found between accommodation preference and feeding preference. The majority of the rooming-in group preferred breast feeding; the majority of the nursery group preferred bottle feeding.

2. A highly significant relation was found between accommodation preference and patient's parity. On the whole, the rooming-in group members have lower parities than the nursery group members.

3. No relation was found between accommodation preference and patient's age.

4. A highly significant relation was found between accommodation preference and occupation of patient's husband. The preponderance of patients in upper occupational classifications (student, professional, small business) occurred in the rooming-in group. If the student classification is not included, the groups approach similarity.

5. A highly significant relation was found between accommodation preference and patient's education. The preponderance of patients in higher educational classifications (college and above) occurred in the rooming-in group.

6. No statistically significant relation was found between accommodation preference and patient's descent, though a trend approaching significance was noted for rooming-in to be chosen oftener by patients of the United States, British Isles, and Northwest European descent, and nursery, by patients of Southern European descent.

7. No relation was found between accommodation preference and patient's religion.

8. A highly significant relationship was found between accommodation preference and patient's race. The rooming-in group contained fewer Negro mothers in proportion to white mothers than did the nursery group.

During the two-year period, screening interviews were obtained on 280 private patients. As this group was a biased sample, the data were not analyzed statistically. Compared with clinic patients, preferring rooming-in, the private patients more consistently preferred breast feeding, represented a different cultural and economic group, but were similar to the clinic group in age and parity.

FROM THE AUTHORS' SUMMARY.

OPTIMAL METHODS IN THE TREATMENT OF OPHTHALMIA NEONATORUM. ARNOLD SORSBY and IRIS KANE, Brit. M. J. **2**:562 (Sept. 10) 1949.

Sorsby briefly reviews his results with the sulfonamide drugs and with penicillin and finds that the percentage of failures was considerable in both series. In the present study, he reports on 151 new cases, with the following results: The intensive local application of penicillin is still the best mehod of penicillin therapy of ophthalmia neonatorum. The sulfonamides may be used to advantage in higher doses and a more rapid response is obtained, the results being as rapid as those obtained with the intensive local use of penicillin. Contrary to expectation, the combined local use of penicillin and oral administration of the sulfonamides did not seem to reduce the rate of relapse. Sulfamerazine is the sulfonamide of choice, as with it the frequency of unsatisfactory responses and relapses is reduced.

The routine procedure of treatment for both methods is then described. In a summary, it is stated that the oral administration of doses of 200,000 units of penicillin, either alone or after an initial intramuscular injection, has proved disappointing. The duration of the treatment was reduced by increasing the dose of the sulfonamide. Combined oral administration of the sulfonamide and local use of penicillin proved effective in reducing the duration of the treatment, but was ineffective in reducing the considerable frequency of relapses. The authors believe that the best way of administering penicillin is the instillation of drops in a concentration of preparation of 10,000 units per milliliter at intervals of one minute to one-half hour, and then at less frequent intervals. The best results with sulfonamide therapy were obtained with higher doses, i. e., sulfamerazine in a dose of 0.5 gm. initially and then 0.25 gm. at intervals of eight hours.

ARNOLD KNAPP [ARCH. OPHTH.].

AUTOMATIC ACTS OF THE NEWBORN. ANDRÉ THOMAS and F. HANON, Rev. Neurol. **79**:641 (Oct.-Nov.) 1947.

Thomas and Hanon report the study of the behavior of the newborn infant by motion-picture analysis. Immediately after delivery the infant holds its arms in abduction in an attitude of crucifixion for a short time. The authors note that this has the effect of expanding the chest, as by the mechanism of artifical respiration, and is probably a response to anoxia. Standing responses and walking movements can be elicited as early as the first day by supporting the trunk and taking care of coordination in the act of walking. The head flops loosely on the shoulders in an erect position but resists movements in various directions when the infant is horizontal. The trunk and the arms which are kept usually in the fetal position, resist passive movement and restore themselves to this position. Various stimuli bring about quick extension of the arms from their normal resting position in the fetal attitude; this is the first part of the Moro reflex. The stimulus of altering the infant's position in space is apparently not sufficient to bring this about; backward displacement of the head is necessary, though the reaction has been brought about by other stimuli. The infant extends its arms and head in forcible crying. Once the reflex of arm extension has been elicited, it can be abolished by flexing the head on the trunk.

The authors note the complex synergistic response of the infant's mouth, lips, tongue, head, and neck in orienting to the tactile stimulus on the face in the first part of the sucking reflex, which is completed by taking the stimulus object into the mouth. They note that the response started by the tactile stimulus cannot be considered a reflex, but, rather, as behavior oriented in time and space.

Further complex behavioral responses, such as the removal of a noxious stimulus from the foot by means of cross extension responses of the other side, are noted. Also noted is the constant response of incurvation of the trunk in response to stimuli in the lumbar region.

On the basis of this study, the authors point out the innate capacity of the infant for behavior oriented toward time and space from the very first hours of life.

LEGAULT, Washington, D. C. [ARCH. NEUROL. & PSYCHIAT.].

RH INCOMPATIBILITY AND MENTAL DISEASE (ENCEPHALOPATHIES AND OLIGOPHRENIAS). MANUEL FRANCISCO BECA, Rev. psiquiat. **11**:51, 1946.

Beca reports five cases of double athetosis with mental deficiency. In one case there was also spastic tetraplegia, and in another there were cerebellar signs. In each case the mother was Rh negative and the child Rh positive. In two cases there was a suggestive history of erythroblastosis in the children, and in one case, a familial history of erythroblastosis.

N. SAVITSKY, New York [ARCH. NEUROL. & PSYCHIAT.].

Acute Contagious Diseases

POLIOMYELITIS: EARLY DIAGNOSIS AND EARLY MANAGEMENT OF ACUTE CASES. JOHN R. PAUL, Ann. Int. Med. **30**:1126 (June) 1949.

Paul is concerned with the early aspects of the diagnosis and therapy of poliomyelitis. He stresses the term "early" as meaning that period often before the patient reaches the hospital, because at that stage of the illness the critical period is usually already passed. He quotes Russell's statement that "the battle to decide the fate of the spinal cord cells is probably over before the paralysis is detected."

There has been some change in the clinical picture and in the epidemiology of the disease during the past years. The age of the average patient with poliomyelitis tends to be older than it was a generation ago. In this sense the disease is no longer "infantile paralysis." There is no explanation for this shift in the behavior of the disease other than it is due in part to shifts in the age composition of the populations involved. The clinical implication, however, is clear in that adult poliomyelitis is becoming commoner. Moreover, cases of the nonparalytic disease are more commonly reported, but this does not necessarily mean that there is a real increase in the incidence of this type; rather, the increase may be attributed to the fact that these cases receive more clinical attention than they did heretofore.

Paul stresses the fact that the symptomatology of acute poliomyelitis differs in different age groups and that the so-called diphasic course, which is classic for children, is certainly less common in persons above the age of 14. Pain in the back and an insidious onset are likelier to occur in patients past the age of 15. There are many cases, particularly among the older adolescent and the younger adults, in which the disease has been called the "straggling type of poliomyelitis." This rather poor term expresses how the patient drags along for a few days, with doubt as to the diagnosis. For early and accurate diagnosis, one must not depend on the typical symptoms presented by the small child if one is to detect the disease in older children and in adults.

One cannot be didactic about the treatment of poliomyelitis, particularly in the earlier stages. During epidemics the most astute clinician cannot determine during the first hours or days whether a given patient whose initial symptoms are limited to sore throat, headache, fever, and vomiting will or will not have paralysis. However, the physician's responsibility lies in the management of patients of any age who may be in the early stages of abortive or paralytic poliomyelitis. Paul states that all persons with brief febrile illnesses occurring during an epidemic of poliomyelitis should be regarded with suspicion and their physical activities curtailed, and that they should be treated more cautiously than usual and kept under observation about 10 days. There is, moreover, a theoretical public-health aspect of the nonparalytic case. The degree of paralysis or the severity of involvement of the central nervous system bears no direct relation to the excretion of virus in the mouth or the intestinal tract.

"It is not necessary for the attending physician to make a public diagnosis of poliomyelitis in order to observe a suspicious case for a week or 10 days. Indeed the physician may not care

to mention the possibility of poliomyelitis to the family, for families are prone to be apprehensive to the point of hysteria during an epidemic and anything which minimizes commotion is desirable. The local health officer may also object if the diagnosis is made too freely or made in the absence of orthodox diagnostic criteria. But this caution does not detract from the desirability of observing early and questionable cases most carefully for the development of secondary phase signs, and of regulating their physical activity."

Paul does not recommend that all nonparalytic patients be hospitalized; the decision as to hospitalization of patients with the milder disease varies in different places and during different epidemics and should certainly depend on the individual patient, the local facilities for hospitalization, and the facilities for observing the patient at home. The author states that a special isolation hospital is not necessary for poliomyelitis patients and that general hospitals can care for them and should accept their community responsibility to do so.

There is no specific therapy. Antipoliomyelitis serum, chemotherapy, and antibiotics do not seem to offer much. Strong analgesics are not very effective in the control of the pain, and the application of moist heat remains the most practical method of combating pain. Paul has had little direct personal experience with the use of neostigmine and curare, and he is inclined to regard the use of both these drugs as still in an experimental stage. He goes on to state, "Any physician who has much to do with the clinical responsibilities in this disease knows full well of the presure which is brought to bear by parents and well meaning friends, to do something definite, something positive or even new and spectacular in the way of treatment. My own feeling is that all meddlesome forms of therapy should be avoided because of their potential traumatic effect. Therapy which includes the use of strong purgatives seems to be contraindicated."

Many aspects of therapy fall within the province of the orthopedist and belong in the category of after-care. Management of the bulbar form of the disease, in which the air passages must be kept as free from secretions as possible by postural drainage, suction, and, as a last resort, tracheotomy, presents special problems, as does the use of the respirator.

In conclusion, Paul stresses the fact that, certainly during epidemics at least, it is expected that a team can best perform the tasks of management of poliomyelitis patients. He thinks that this team may best be composed of an orthopedist, a physical therapist, specially trained nurses, and others. The physician is to remain in charge of the situation until the disease has definitely gone into the stage of after-care, and he should be on the alert to guard his patient from unnecessary trauma, exertion, and, above all, meddlesome therapy. The early treatment of poliomyelitis calls for an alert physician, whose major responsibility is to guard his patient and be ready for any serious emergency.

GUTTMAN, Wilkes-Barre, Pa. [ARCH. NEUROL & PSYCHIAT.].

ENCEPHALITIS FOLLOWING VACCINATION AGAINST PERTUSSIS (EDITORIAL). Ann. Int. Med. **32**:343 (Feb.) 1950.

Recent observations indicate that grave injury to the nervous system, with symptoms resembling those described in postvaccinal encephalitis, may follow the adminitration of pertussis vaccine. The first systematic study was that of Byers and Moll, who reported 15 cases over a period of 10 yr. Symptoms appeared after an interval of 20 min. to 72 hr. following the injection. The onset was usually abrupt, with high fever, restlessness, irritability, or drowsiness, followed quickly by generalized, or occasionally unilateral, convulsions and coma. Usually there were evidences of gross organic cerebral lesions.

All 15 patients reported by Byers and Moll survived the acute illness, which subsided after two to 10 days. Two subsequently died of pneumonia, after periods of progressive deterioration. Of the 13 surviving children, only one showed reasonably satisfactory recovery; in three instances the interval was too short to warrant final conclusions, but in the nine others there were serious, and almost certainly permanent, sequelae, of varying severity.

The pathogenesis of this form of encephalitis is still not established. The close similarity of the encephalitic lesions in this disease and those in the encephalitis accompanying vaccinia, antirabies vaccination, smallpox, chickenpox, and measles suggests, although it does not prove, that the same mechanism is involved in the production of them all. The rarity of these attacks strongly suggests that, whatever the mechanisms, they must depend in part on some individual peculiarity or predisposition.

The administration of pertussis vaccine involves a definite, but remote, risk of producing a damaging encephalitis. This encephalitis is comparable in its incidence to the encephalitis following smallpox vaccination; its immediate mortality has been less, but the frequency of severe permanent injury to the brain has been higher. The mortality of pertussis in young children is so high, however, and the protective value of the vaccine so well established that the remote risk of encephalitis should not interfere with the widespread use of the vaccine.

Certain precautionary measures, however, are indicated. All patients should be observed after administration of the vaccine and further doses withheld if severe reactions occur, particularly if there are convulsions or any other reasons to suspect cerebral injury. As a rule, the vaccine should not be given to children with fever or other evidence of acute illness, to patients with evidence of cerebral damage of other type, or to those who have shown manifestations of hypersensitivity.

ALPERS, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

TREATMENT OF CHRONIC NASAL DIPHTHERIA CARRIERS: REPORT OF CASE. JOSEPH X. MEDWICK and OLAV E. HALLBERG, Ann. Otol. Rhin. & Laryng. **57**:135 (March) 1948.

The finding of a fetid, irirtating unilateral or bilateral discharge from the nose causing excoriation and swelling of the alae nasi and upper lip should suggest the presence of diphtheria organisms. Since all strains of the diphtheria organism are not pathogenic, it is necessary to test the virulence of the culture obtained. There is considerable evidence that a patient may acquire a virulent strain and carry it in the nose indefinitely without clinical evidence of toxic effects, a condition ascribed to autoimmunization. The virulence of the organisms in the nose may become attenuated so that they are harmless, but at some future time they may again become virulent, owing either to local trauma or to infection with other bacterial forms. Treatment of nasal-diphtheria carriers with antiseptic nose and throat sprays and by painting the throat with solutions of iodine or formaldehyde has not been satisfactory. Diphtheria antitoxins have given little success, probably because they exert no direct action on the organisms themselves. Tonsillectomy and adenoidectomy combined with use of sprays of an antiseptic solution or chemotherapeutic agents frequently have proved useful. Roentgen radiation, sulfonamides, and penicillin are usually effective in the treatment of chronic nasal-diphtheria carriers. However, the presence of chronic sinusitis in a nasal-diphtheria carrier is an indication for surgical treatment combined with chemotherapy. Despite the infrequency of the occurrence of diphtheria organisms among nonimmunized patients who have a chronic nasal infection, material from the nose should be cultured for these organisms. Cured carriers should be checked periodically, especially after severe infections of the upper respiratory tract.

MILLER, Philadelphia [ARCH. OTOLARYNG.].

TONSILLECTOMY AND POLIOMYELITIS. DANIEL S. CUNNING, Arch. Otolaryng. **46**:575 (Nov.) 1947.

The suggestion was made at the May 1946 meeting of the American Laryngological, Rhinological and Otological Society that a nationwide survey be conducted to determine the relation of tonsillectomy to poliomyelitis. Members of the society in each state were appointed to gather pertinent information for a statistical report. Some made no reports; others made reports so sketchy and incomplete as to be useless. Almost 4,000 of the 6,000 questionnaires returned had to be discarded. Although the study cannot settle conclusively the problem whether surgeons should avoid removing tonsils during epidemics of poliomyelitis, some valuable evidence was obtained. For instance, in 4.7% of the cases of bulbar involvement the illness was preceded by tonsillectomy, while in only 1.9% of the cases of spinal involvement did the poliomyelitis follow recent tonsillectomy. Even these values must be considered inconclusive because of inadequate data and lack of comparative values.

The surgeon must decide whether it is better to perform tonsillectomies in the summer months, when the incidence of infections of the respiratory tract is lowest, or to avoid the period of epidemics of poliomyelitis and run the risk of increased infections of the respiratory tract. Since most tonsillectomies are necessary surgical procedures in the interest of preventive medi-

cine, the operation should not be postponed because of an unfounded fear of poliomyelitis. To aid in answering this question, Cunning urges that a study be made on children who are to be tonsillectomized this summer to determine whether they are more likely to contract poliomyelitis than nontonsillectomized children.

RYAN, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

TRACHEOTOMY IN POLIOMYELITIS. R. J. STROBEL and N. CANFIELD, Arch. Otolaryng. **52**:341 (Sept.) 1950.

Strobel and Canfield discuss the indication for tracheotomy under two heads: 1. Therapeutic tracheotomy should be considered whenever (*a*) any respirator patient exhibits signs of bulbar involvement or displays persistent cyanosis or struggling (restlessness and combativeness usually mean air hunger), or (*b*) any nonrespirator patient is unable adequately to keep his airway free of secretions, as evidenced by moist rales, choking, and cyanosis.

2. Prophylactic tracheotomy should be seriously considered whenever (*a*) early and progressive bulbar signs are present and before the patient has difficulty, and (*b*) a long siege in the respirator seems probable, even though no bulbar signs are present. A patient with severe respiratory paralysis may have difficulty in handling pharyngeal mucus because of inability to cough effectively.

Tracheotomy was performed on 10 patients with bulbar poliomyelitis. Five of the patients died. In all surviving tracheotomized patients the tracheotomy was probably a lifesaving procedure. Earlier tracheotomy for three of the five who died might have been lifesaving. The authors state that the otolaryngologist should be consulted immediately concerning every patient with poliomyelitis who shows symptoms of bulbar involvement or respiratory difficulty.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

USE OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) IN POLIOMYELITIS. L. L. CORIELL, A. C. SIEGEL, C. D. COOK, L. MURPHY, and J. STOKES JR., J. A. M. A. **142**:1278 (April 22) 1950.

Certain data on poliomyelitis suggest an unusual host-parasite relation. Many observations indicate that susceptibility or resistance to poliomyelitis involves nonspecific defensive mechanisms and, indirectly, that the host response is more important than the virulence of the virus in determining the course of infection. Rapid mobilization of bodily defensive mechanisms may limit the spread of infection in the usual nonparalytic case, whereas a slower response as a result of constitutional factors or exhaustion may permit infection to spread. It is not known whether or not poliomyelitis precipitates an "alarm reaction." Corticotrophin (ACTH) induces this reaction quickly. It occurred to the authors that a failure of these mechanisms to act naturally might contribute to the development of paralytic poliomyelitis.

The therapeutic use of corticotrophin was observed in a group of 70 patients who had been ill less than five days, 35 receiving corticotrophin and 35 a placebo.

It was found that the "alarm reaction" is mobilized in poliomyelitis, as shown by the eosinophile response. In these patients corticotrophin produced a physiologic effect, as evidenced by a further depression of the eosinophile count and by increased excretion of 17-ketosteroids. There was no demonstrable effect in the treated as compared with the untreated group when evaluated on the basis of (1) temperature response, (2) paralysis, (3) progression of paralysis, or (4) early residual effects.

Coriell's statistical analysis shows clearly that corticotrophin has no beneficial or obvious deleterious effect on the course of poliomyelitis when treatment is begun after the onset of symptoms.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CLINICAL MANAGEMENT OF ACUTE POLIOMYELITIS. E. SMITH, D. J. GRAUBARD, J. FALCONE, T. B. GIVAN, P. ROSENBLATT, and A. FELDMAN, J. A. M. A. **144**:213 (Sept. 16) 1950.

At present there is no form of treatment of acute poliomyelitis that limits the spread of virus in the central nervous system or alters its effect on the nerve cells. In the past few years there has been an increasing interest in the control of pain and vasomotor instability. Various

means of sympatholysis have been tried to correct the vasomotor dysfunctions. Maintenance of circulation in the muscle aids in its rehabilitation, and the degree of recovery is directly related to the time of institution of corrective measures.

In the present study the objective has been to shorten the duration of pain, muscular spasm, and vasomotor instability during the acute and subacute stages of poliomyelitis so that measures of rehabilitation of the patient can begin as early as possible. During 1949, 663 patients with acute poliomyelitis were treated with priscoline® (2-benzyl-2-imidazoline hydrochloride), a sympatholytic drug. Smith and his colleagues believe that priscoline® was a useful adjuvant in the early management of the disease. The benefits to treated patients included the relief of pain, spasm, and vasomotor dysfunction. In the doses described, morbidity was minimal.

Nearly all patients manifested some form of progress, and their clinical status improved so rapidly that it was possible to transfer the majority of them, relaxed and free of pain, to their homes or to orthopedic hospitals in seven to 14 days. The nursing personnel was relieved of the tremendous patient load that they would have had if treatment with hot packs had been used. Results such as these had not been accomplished in the past with any other form of symptomatic therapy. The further investigation of priscoline® and other sympatholytic drugs is indicated.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

DOES MODIFIED MEASLES RESULT IN LASTING IMMUNITY? SAMUEL KARELITZ, J. Pediat. **36**:697 (June) 1950.

Karelitz questioned pediatricians, general practitioners, epidemiologists, and the distributers of prophylactic agents for measles. The answer was that modified measles does result in lasting immunity for most persons. In the few who have suffered second attacks, the severity of the recurrence was not dependent upon the degree of modification originally produced.

MACDONALD, Pittsburgh.

SOME DEBATED POINTS IN THE TREATMENT OF ACUTE POLIOMYELITIS. PHILIP M. STIMSON, J. Pediat. **36**:704 (June) 1950.

Stimson says that moving patients with early poliomyelitis long distances may do more harm than good. He also protests the use of lumbar puncture except when it is necessary to establish a diagnosis in early questionable cases. He discusses the pros and cons of the use of dehydration and the perscribing of sedatives and antispasmodics. The management of urinary retention, the head-down position in postural drainage, the warming of oxygen, the use of artificial respiration, and the advantages of the tilt table are also debated. He says that most Eastern clinicians believe that tracheotomy should be avoided if possible. Many other clinicians, particularly those west of the Mississippi, favor tracheotomies in bulbar and bulbospinal poliomyelitis cases. There is, however, a general tendency throughout the country to do fewer tracheotomies. Finally, he states that treatment that is not indicated is contraindicated.

MACDONALD, Pittsburgh.

PRISCOLINE FOR PAIN IN POLIOMYELITIS. WILLIAM A. REILLY and ARDWIN H. BARSANTI, J. Pediat. **36**:711 (June) 1950.

The authors used 2-benzyl-2-imidazoline hydrochloride (priscoline®) in an attempt to control reflex spasm and pain in poliomyelitis. Thirty-five patients were treated. Less than 25% were definitely benefited; almost 50% were not benefited at all. The results in the others were equivocal. One patient with tetanus was not helped by priscoline.®

MACDONALD, Pittsburgh.

SERUM POTASSIUM IN POLIOMYELITIS. ALEXANDER M. EARLE, J. Pediat. **36**:715 (June) 1950.

On the basis of studies on 32 patients with poliomyelitis, Earle says that there is no correlation between serum potassium levels and the severity of the paralysis. Ten patients had low potassium levels; all had severe paralysis or bulbar involvement. Potassium chloride given orally to these patients did not lessen the degree of paralysis, and the number of patients involved is too small to justify any conclusions.

MACDONALD, Pittsburgh.

ANTIBIOTIC SPECTRUM OF HEMOPHILUS PERTUSSIS. EDWARD B. WELLS, CHANG SHIH-MAN, GEORGE G. JACKSON, and MAXWELL FINLAND, J. Pediat. **36**:752 (June) 1950.

Antibiotic sensitivity of each of a group of recently isolated strains of Hemophilus pertussis was tested in vitro. On a weight basis, the order of effectiveness of these antibiotics was the following: (1) polymyxin D, (2) aerosporin® (polymyxin B), (3 to 5) chloramphenical (chloromycetin®), aureomycin, and terramycin, which have very similar activity against the great majority of the strains, (6) penicillin, (7) streptomycin, (8) neomycin, and (9) bacitracin. These results are only a preliminary means of comparison. The real values of these antibiotics can be obtained only by direct clinical trials under controlled conditions.

MACDONALD, Pittsburgh.

NEWER KNOWLEDGE ON THE PATHOGENESIS OF POLIOMYELITIS. CLAUS W. JUNGEBLUT, J. Pediat. **37**:109 (July) 1950.

Jungeblut says that poliomyelitis is one of the most widespread communicable diseases of childhood. Those cases with central nervous system involvement are exceptional (perhaps about 10% of all poliomyelitis cases) and are comparable in biological significance to measles or mumps encephalomyelitis. There is abundant clinical and laboratory evidence that the poliomyelitis virus is not especially neurotropic but is pantropic. You can, if you wish, find evidence that the virus affects the intestinal musculature, the myoneural junctions, the skeletal muscle, and the myocardium. It is true that once the central nervous system is invaded, the virus acts as if it were strictly neurotropic, and here destruction of the ganglion cells is irreversible. But the virus responsible for the initial systemic phase of the disease (a poorly defined phase, by the way) cannot be considered neurotropic in the strict sense of the word. Jungeblut supposes that perhaps the virus occurs in more than one form, blending into strains with viscerotropic and neurotropic phases. Thus, the term "poliomyelitis" may include a number of conditions ranging from almost imperceptible extraneural involvement through reversible pathologic changes at the myoneural junction to the irreversible change in the ganglion cells of the anterior horn.

He suggests that the infection may progress in these stages: First the virus enters the alimentary tract, penetrates the intestinal mucosa, and begins to grow within the wall of the intestine. Up to now no symptoms have been produced. In the second stage, local mechanisms of defense in the lymphatic system break down; the virus escapes into the blood stream for a transient period and then is removed by filtration and is fixed in muscle tissues. As the virus multiplies in skeletal and heart muscle, various peripheral lesions may occur (e. g., myocarditis). Symptoms of these peripheral lesions may appear but are not irreparable. The third and final stage would occur only in those exceptional cases in which, after excessive growth, the virus crosses the myoneural synapsis, travels along the peripheral nerves to the spinal cord, and irreparably destroys the ganglion cells in the anterior horn.

Jungeblut does not say that this is the way it happens. He says that this is the way it might happen. There are wide gaps in our knowledge. In any event, poliomyelitis is not strictly a central nervous system disease.

MACDONALD, Pittsburgh.

A COMPARISON OF "SYMPTOMATIC TREATMENT," GAMMA GLOBULIN, AND PENICILLIN IN THE TREATMENT OF SCARLET FEVER. LOUIS WEINSTEIN, and SAMUEL F. POTSUBAY, J. Pediat. **37**:291 (Sept.) 1950.

Weinstein and Potsubay studied 255 cases of scarlet fever. Alternate patients were given gamma globulin, one dose intramuscularly; penicillin, 15,000 units intramuscularly every three hours for 10 days, or only "symptomatic treatment," consisting in such measures as bed rest and throat irrigations. Gamma globulin caused rapid fading of the rash and rapid relief of nausea, vomiting, and generalized aching. It had little or no effect on the development of complications.

Penicillin is the best treatment for scarlet fever. It rapidly cleared streptococci from the throat and significantly lowered the incidence of suppurative complications. In a number of penicillin-treated patients, whose throats had been cleared of streptococci, reinfections developed, with and without symptoms, probably because of contact with acute disease or with carriers.

MACDONALD, Pittsburgh.

AUREOMYCIN IN THE TREATMENT OF PERTUSSIS: A PRELIMINARY REPORT. WILLIAM J. MILLER and JOHN E. ROSS, J. Pediat. **37**:307 (Sept.) 1950.

Miller and Ross treated patients with pertussis with aureomycin in doses of 350 mg. per kilogram of body weight. The drug was given for as long as eight to 10 days. The patients improved gradually and steadily after treatment was started. Diarrhea and irritation of skin and mucous membrane developed in two patients from the drug. These symptoms cleared when administration of the drug was stopped. The authors suggest that doses of 100 mg. per kilogram a day may be more satisfactory.

MACDONALD, Pittsburgh.

POLIOMYELITIS-TONSILLECTOMY SURVEY—YEAR 1949. DANIEL S. CUNNING, Laryngoscope **60**:615 (July) 1950.

Dr. Cunning's completed report on the tonsillectomy-poliomyelitis question includes over 36,000 cases of poliomyelitis and nearly 100,000 cases of tonsillectomy compiled over a four-year period. There was no definite casual relation found. However, it was concluded that tonsillectomy, or for that matter any elective operation, should not be performed during a poliomyelitis epidemic or any other epidemic and, conversely, in the absence of an epidemic, tonsillectomy should not be postponed during the summer months merely because poliomyelitis is likely to occur then.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

SMALLPOX VACCINATION WITH PROLONGED VACCINIA. JOHN A. BIGLER, and EUGENE L. SLOTKOWSKI, Pediatrics **7**:24 (Jan.) 1951.

Definite clinical, histologic, and immunologic changes take place after smallpox vaccination. After full development of the vaccinial lesion, on the ninth or 10th day, drying, crusting, and scarring follow. Histologically, there are degenerative and irritative changes in the epidermis believed to be due to the direct action of the virus on the epithelial cells. Immunologically, humoral antibodies to vaccinia begin to appear at the end of the first week following cutaneous vaccination, increase in amount during the second and third weeks, and reach a maximum at the end of the third week. The probable reason for involution of the vaccinial lesion after the pustular stage is the appearance of specific antibodies in the blood which apparently neutralize the vaccinia virus. The presence of histologically active vaccinial lesions approximately four months after implantation of the vaccinia virus could be explained only on an inability to develop immunity to vaccinia virus. Because of this lack of immunity, degenerative action of the vaccinia virus continued unopposed in the case reported, and death occurred.

FROM THE AUTHORS' SUMMARY.

USE OF THE PERTUSSIS AGGLUTINOGEN SKIN TEST IN A WELL BABY CLINIC. NOAH BARYSH, Pediatrics **7**: 48 (Jan.) 1951.

Intradermal skin tests with pertussis agglutinogen were performed on 234 infants. In one group of 100 infants tested with this material at least three months after pertussis prophylaxis, it was found that 92% had positive (immune) skin reactions. In a second group, of 134 infants skin tested prior to pertussis vaccination, 83% (111) had negative skin reactions. Sixty-six of these 111 infants were tested after pertussis prophylaxis; in 92% a positive skin response developed.

The pertussis agglutinogen skin test can be used to determine the efficiency of materials used for pertussis prophylaxis. It is a reliable indicator of the immune response of an infant to Hemophilus pertussis immunization and is recommended as an effective agent for determining the susceptible infant—one lacking the minimal clinical protection against pertussis—after pertussis vaccination.

FROM THE AUTHOR'S SUMMARY.

ACUTE ANTERIOR POLIOMYELITIS IN 1947 WITH SPECIAL REFERENCE TO LONDON. ALAN DALEY, Proc. Roy. Soc. Med. **41**:52 (Jan.) 1948.

In 1947 England had the largest epidemic of poliomyelitis in its history. Assuming notification of cases to be a rough guide to incidence, the most interesting features in recent years in England and North America are (1) a shift toward the older age groups and (2) an increase in the cases of brain stem involvement. There is evidence that more persons now reach adolescence or adulthood without acquiring immunity because of better standards of sanitation. This is suggested by the minimal incidence of poliomyelitis among adults in Japan, its frequent occurrence in the American occupation forces, and the predominance among children under 5 yr. of age in endemic areas, such as Malta and Mauritius. In St. Helena, however, where the disease was previously unknown, the highest incidence was in the age group of 10 to 25 yr. The adult is likelier to have the bulbar type.

The human patient or carrier provides the two important means of spread: droplets from the nasopharynx and excreta.

A reservoir of poliomyelitis has always existed in London, with the seasonal peaks about mid-September, most cases occurring between July and the end of November. Up to Oct. 25, 1947, 908 cases were reported in London, more than in the entire decade of 1937 to 1946. Whereas in the preceding decade 78% of the patients were under 15, in 1947 this figure was 64%. Among patients under 15, there was an excess of males of 1.23:1. Comparison of the incidence for each metropolitan borough showed that boroughs with a significantly higher rate were surrounded by boroughs in which the incidence was close to the average for London as a whole and which were clearly "isolated areas for high incidence." Several possible factors to account for this difference are discussed and discarded as without proof: (*a*) more complete notification, or overnotification; (*b*) social conditions; (*c*) differences in immunity level, and (*d*) differences in method of control.

Age Incidence.—In the age group of less than 5 yr., there was a drop from 55%, in 1921-1923, to 27.4%, in 1947, the latter despite a reversal in the population trend, suggesting either a change in the virus to which older age groups are susceptible or increasing immunity in infants.

Overcrowding.—The risk of multiple cases in a family is 3%, indicating that contact is not important, that the rest of the family is immune, or that, although the whole household is infected, only one clinical case develops. There is statistical evidence that true paralytic poliomyelitis is less common in overcrowded households.

The histories of contact and exposure of 391 hospitalized patients offered little or nothing of value.

General Epidemiological Considerations.—"Very few lessons have emerged from our analysis. We do not know why the disease was so much more prevalent in England in 1947 than ever before. . . . Authentic cases are reported of second attacks." There is a suggestion that a larger proportion of the population had failed to be immunized in infancy, possibly because of improved sanitation.

Of 391 cases analyzed, confirmed hospital cases, 34.8% were of the abortive and 8.5% of the bulbar type. The case mortality was 5.1%; the incidence of complete recovery was 54.2%. In 6% of the cases a respirator had to be used at one time or another. It is estimated that 25% of patients will have a limited working capacity and that the working capacity of 5% of the 391 patients will be almost nil.

BERRY, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

INVOLVEMENT OF EYES IN POLIOMYELITIS. R. COLLIN and W. L. BASSENGE, Klin. Monatsbl. Augenh. **113**:255, 1948.

Collin and Bassenge made ophthalmologic studies on 40 patients who had received treatment in the "iron lung" in the course of the epidemic of poliomyelitis in Berlin in 1947, in which a total of 2,300 cases were reported. Seventy other patients with poliomyelitis who did not require treatment in the "iron lung" were also given a thorough examination of the eyes. The ophthalmologic examination was repeated at regular intervals, so that it was often possible to observe the appearance and rapid disappearance of symptoms. A third group, of 40 patients, who had persistent spinal paralysis after an attack of poliomyelitis were examined for late ocular symptoms. Three and one-half months was the time that had elapsed after the acute attack. Involvement of

the eyes is not rare in poliomyelitis. Nuclear and supranuclear paralysis of the facial nerve, ptosis, abducens paralysis, and paralysis of the internal rectus muscle were observed. There is a good prospect that these types of paralysis will subside. In the cases of poliomyelitis in which lesions exist in the upper part of the spinal cord, involvement of the sympathetic fibers may produce disturbances in the pupils. The majority of the patients who required treatment in the iron lung showed signs of stasis in the retinal vessels and in the optic papilla. Although optic neuritis was not encountered during this epidemic, it may be expected to occur. The authors believe that in patients with obscure paralysis of some of the cerebral nerves poliomyelitis should be considered. It is advisable to hospitalize these patients, not only for prevention of further spread of the poliomyelitis but also for the special care which may become necessary, since the lesion is close to the respiratory center.

J. A. M. A.

Specific Prophylaxis of Postdiphtheritic Paralysis. E. Lorenz, Wien klin. Wchnschr. **61**:12 (Jan. 7) 1949.

During a period of one and a half years, diphtheria antitoxin was administered intraspinally in addition to intramuscularly or intravenously. The frequency, severity, and duration of paralyses were definitely decreased as compared with the corresponding findings for a control group of children who did not receive the antoxin intraspinally. The children given intraspinal treatment showed an incidence of neurologic involvement of 43.2% and no neurologic mortality, as compared with an incidence of involvement of 60.9% and 8 fatal cases for the control group. The duration of the paralytic phenomena was reduced by half.

Mason, Brooklyn [Arch. Neurol. & Psychiat.].

Acute Infectious Diseases

Production of Rheumatic Subcutaneous Nodules. S. Schwartz and O. Steinbrocker, Am. Heart J. **40**:100 (July) 1950.

The production of rheumatic subcutaneous nodules was attempted in 39 patients with rheumatoid arthritis, in 18 patients with rheumatic fever, and in 15 normal controls (1) by the injection of whole blood over the olecranon, applying friction to the area receiving the injection; (2) by injecting a solution of trypsin over the olecranon, and (3) by injecting joint fluid over the olecranon from a patient with active rheumatoid arthritis and applying friction. Patients in various stages of the disease, active and inactive, with and without naturally occurring nodules, were used. No nodules were produced experimentally in any case.

From the Authors' Summary.

Use of Chloromycetin in Infections: I. In Nonbacterial (Atypical Undifferentiated Respiratory Infections). Philip Cohen and Ralph Schwartz, J. Pediat. **37**:23 (July) 1950.

Cohen and Schwartz gave chloramphenicol (chloromycetin®) to children with nonbacterial or virus respiratory infections. The drug produced no toxic manifestations when given in a dose of 100 mg. per kilogram a day until fever disappeared and then 50 mg. per kilogram a day until temperature was normal for four days.

Chloramphenicol was very effective in most cases of atypical pneumonia and in most cases of virus infection of the upper respiratory tract with systemic symptoms. Although the drug was only partially effective in laryngotracheobronchitis, its use is recommended because of apparent amelioration of respiratory distress.

If chloramphenicol is discontinued in less than six to seven days in these respiratory infections, relapses or recurrences may occur.

Macdonald, Pittsburgh.

Congenital Malaria. B. S. Jones, Brit. M. J. **2**:439 (Aug. 19) 1950.

This article gives a brief review of the literature of reported cases of congenital malaria. The latest complete review listed is by Chen and appeared in the *Chinese Medical Journal* in 1944. Chen summarized 39 cases of congenital malaria from the world literature. Most British

and American authors still believe, however, that congenital transmitted malaria is a rarity. It is felt by Jones, however, that in certain parts of the world it should be suspected when infants begin to run high temperature and vomit in the first few days of life.

Jones reports three patients all of whom died in spite of therapy for malaria parasites. In all three cases malaria parasites were found in the blood of the newborn baby, and in one case postmortem hepatic puncture revealed malaria parasites.

In the discussion the author states that most of the cases of congenital malaria involve European women who have fairly recently moved into the tropics and whose immunity is very low.

In conclusion it is suggested that "with the increasing degree of immunity to malaria the frequency of infection of the placenta rises, while coincidentally the efficiency of the placenta as a barrier to foetal transmission increases and the incidence of congenital malaria falls."

BIRDSONG, Charlottesville, Va.

THE GENERAL MANAGEMENT OF RHEUMATIC FEVER. E. G. L. BYWATERS, Proc. Roy. Soc. Med. **43**:199 (March) 1950.

Apart from the chemoprophylaxis of rheumatic fever and the use of cortisone and corticotrophin, there is really very little on this subject that has not been said by many others in the last 50 yr. There is, however, a fair amount of controversy over some of these traditional lines of treatment. The differential diagnosis is discussed.

Management of rheumatic fever is based on the facts that it is a self-limited disease and that the only sequelae of any importance are the cardiac lesions. Rest minimizes residual cardiac damage. Bed rest is essential until carditis has completely subsided. The sedimentation rate is one of the most useful of the criteria when combined with electrocardiography. Bed rest should be maintained until most or all of the criteria we are using (among which the most useful are sedimentation rate and electrocardiographic change) are met, and then the patient should be gradually mobilized and a close watch kept on these signs of activity.

Salicylates are invaluable in treatment, and the lessening of the fever must reduce the work of the heart. In the cases of severe and active disease with heart failure, salicylates will not arrest the fatal termination. The most spectacular advance in this field is the use of cortisone and corticotrophin, which, though primarily used in rheumatoid arthritis, has been found equally successful in rheumatic fever. Ultimately it may prove that such hormone treatment is more useful in rheumatic fever than in rheumatoid arthritis, since it does not need to be continued for a period of many years.

After discharge of the patient from the hospital, it is important that contact is maintained with the responsible school medical officer, the family doctor, and the referring hospital. This supervision should continue during the next two or three years and preferably through adolescence. General instruction on avoidance of exposure to infection, damp, chills, and limitation of physical activity is necessary.

HEARD, Monterey, Calif.

Chronic Infectious Diseases

GENERALIZED HISTOPLASMOSIS IN INFANTS AND CHILDREN: REVIEW OF TEN CASES, ONE WITH APPARENT RECOVERY. W. G. KLINGBERG, J. Pediat. **36**:728 (June) 1950.

Klingberg describes 10 cases of generalized histoplasmosis. Nine patients died; one apparently recovered. As he describes it, generalized histoplasmosis is a lower respiratory tract disease, with hepatosplenomegaly, anemia, leucopenia, left shift, and, sometimes, thrombocytopenia. The patient who recovered had a positive skin reaction after her acute illness subsided. All the patients who died had negative skin reactions, either because the infection was so overwhelming that no antibodies were produced or because death occurred before there was sufficient time to produce antibodies. Bone marrow culture on Sabouraud's medium is an effective and quick way to prove the diagnosis.

MACDONALD, Pittsburgh.

TREATMENT OF DISSEMINATED HISTOPLASMOSIS WITH ETHYL VANILLATE. AMOS CHRISTIE, JAMES G. MIDDLETON, J. CYRIL PETERSON, and DAVID L. MCVICKAR, Pediatrics **7**:7 (Jan.) 1951.

Some of the physical and pharmacologic properties of ethyl vanillate, a new fungistatic or fungicidal agent, are briefly stated. The records of 12 patients with progressive disseminated histoplasmosis treated with ethyl vanillate are reviewed. Five of these patients are alive and apparently well after treatment, an experience not previously encountered or reported in the literature. The uses of the drug in the treatment of histoplasmosis are outlined, and the toxic manifestations of overdosage are described.

FROM THE AUTHORS' SUMMARY.

VALUE OF PHLYCTENULAR KERATOCONJUNCTIVITIS IN EPIDEMIOLOGY OF TUBERCULOSIS. JUAN MANUEL VILA ORTIZ and JUSTO LOPEZ BONILLA, Arch. oftal. Buenos Aires **23**:184 (July-Aug.) 1948.

The authors state that phlyctenular keratoconjunctivitis is a disease of a predominantly allergic nature. Its origin in the majority of cases is tuberculous, and it should be considered a manifestation of activity, immediate or latent, of a primary infection. A patient with phlyctenular karatoconjunctivitis should always be given a tuberculin test and a roentgenologic examination; these should also be given to the members of his family, as in a high percentage of cases the source of infection can be found among the latter. The authors place special emphasis on this part of the examination.

M. E. ALVARO [ARCH. OPHTH.].

THE PRINCIPLES OF CALMETTE VACCINATION. A. WALLGREN, Paediat. danub. **4**:233 (Nov.) 1948.

Adequate prophylaxis with BCG does not consist only in the vaccination itself. The vaccinated persons should be repeatedly examined as to their sensitivity to tuberculin, and they have to be protected from infection with tuberculosis until their reaction has become positive.

As vaccination of tuberculin-positive persons is useless, only persons giving a negative reaction to tuberculin should be vaccinated. Even with the latter there is always a possibility that the vaccination is performed during incubation of a tuberculous infection.

If a person to be vaccinated has been exposed to infection with tuberculosis, vaccination should be postponed until six weeks after another negative tuberculin reaction has been obtained. Vaccination of infected persons is not harmful, but its result cannot be evaluated.

Positivity to tuberculin following BCG vaccination is of varying duration, extending over two to 10 years. The longer it lasts the more probable it is that the positivity is due to real but latent infection with tuberculosis.

The appearance of a tuberculous process in a child who had been vaccinated with BCG does not mean that the vaccination was useless. Immunity following BCG vaccination is only relative. There are no means to differentiate between immunity developed following infection and the one that appears after BCG vaccination.

For practical purposes it can be supposed that immunity lasts as long as the positivity to tuberculin. Should the formerly positive reaction of a person become negative, immediate revaccination with BCG is indicated.

FROM THE AUTHOR'S SUMMARY.

TUBERCULOSIS OF INFANTS AND SMALL CHILDREN. R. NEUMAN, pediat. listy **4**:11, 1949.

Experience with 44 tuberculous infants in the state children's sanatorium for tuberculosis in the High Tatra shows that tuberculous infants from lower countries bear the tranfser to the highland climate well. The hygienic dietary therapy is completed by small blood transfusions and x-ray therapy. Pneumothorax is without any effect before the first year of life. Of 25 tuberculous infants, 19 were cured, in 5 the state of illness deteriorated and 1 child died.

FROM THE AUTHOR'S SUMMARY.

SUPPURATIVE ADENITIS IN INFANTS VACCINATED WITH BCG BY SCARIFICATIONS. D. E. ZERVOULIAS, Arch. Greek Paediat. Soc. **1**:11 (April) 1947.

Among 2,350 infants vaccinated with BCG by the Rosenthal method, eight suppurations of the glands draining the area of scarifications were observed. In another two infants a swelling of the glands was noticed, but the swelling subsided without suppuration. The suppurated glands were incised, and the discharge continued for two to six months. During this time the general condition was good, and growth was not affected. Examination of the pus and inoculation of this pus into guinea pigs did not reveal the presence of either Mycobacterium tuberculosis or the attenuated tubercle bacilli contained in BCG. Zervoulias discusses the various possibilities regarding the nature of this form of adenitis. It is usually due to the BCG bacillus, but when as in these cases the bacillus cannot be found other factors, unknown for the moment, should be considered responsible.

DOXIADIS, Newcastle, England.

BCG VACCINATION OF EXPERIMENTAL ANIMALS THROUGH THE RESPIRATORY TRACT. M. E. PERDIKOLOGOS, Arch. Greek Paediat. Soc. **1**:45, 1947.

A description is given of a method of vaccinating guinea pigs with BCG through the respiratory tract by using an asthma inhaler or a penicillin nebulizer.

DOXIADIS, Newcastle, England.

A CASE OF TUBERCULOUS HEPATITIS AND ITS BIOLOGICAL REACTIONS. CONSTANTINE V. CHOREMIS and NICOLAOS NINIOS, Acta pædiat. **37**:188, 1949.

A 14-year-old boy had symptoms which suggested an acute liver abscess. Laparotomy was therefore performed. Microscopic examination as well as biopsy proved disseminated tuberculosis of the liver. The following are some interesting points from the examination in this case: 1. Koch's bacillus was abundant in the blood culture. 2. The tuberculin reaction was negative even in a potency of 1:100. It was only after streptomycin treatment that a positive reaction was obtained, but this was still not a strong positive reaction (2+). 3. A high sedimentation rate for erythrocytes was found.

Certain points of view are given about the importance of these biological observations. Treatment in this case was with streptomycin; the total dose administered was 45 Gm. As a result, the patient's temperature dropped and the symptoms of a tuberculous liver decreased. The patient's condition had been normal to the time of writing.

FROM THE AUTHORS' SUMMARY.

POSITIVE GASTRIC CONTENT AND CAVITIES IN CHILDREN. G. J. HUËT, Maandschr. kindergeneesk. **15**:203 (June) 1947.

Tubercle bacilli in the gastric content of children suffering from hilar gland and incipient tuberculosis of the lungs usually disappear with sanatorium treatment in one or, at the most, two years. Some patients, however, need a longer period of treatment, and others never show negative reactions. Four hundred and six patients entered with gastric contents positive for the bacilli; 349 showed negative reactions within two years; 6 within three years, and 5 within six years; 46 continued to show a positive reaction.

Roentgenographic examination of the thorax fails to explain this sufficiently. In such cases the cause may be found in the fact that the disease is hidden behind the heart or liver. It may be that there is only a tuberculous bronchitis. However, one must be aware of another possibility, namely, the presence of a cavity of such small dimensions that it is overlooked. The probability of this explanation is demonstrated in three patients by a series of roentgenograms that show how an obvious initial cavity gradually diminished so far that the small remainder could only be recognized by studying the whole series of roentgenograms. Conservative treatment gives good results in many cases. The collapse therapy is used merely when the cavity is plainly visible for a long time without regression.

VAN CREVELD, Amsterdam, Netherlands.

TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN. S. VAN CREVELD and M. R. H. STOPPLEMAN, Maandschr. kindergeneesk. **17**:77, 1949.

The authors describe their experience with use of streptomycin for treatment of seven children with tuberculous meningitis whose ages varied between 15 months and 6 years. Only one girl was in good condition; she fell ill when 15 months old. Two children survived but showed severe mental defects; their illness began when they were respectively 19 months and 6 years of age.

FROM THE AUTHORS' SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

SURGICAL TREATMENT OF TRICUSPID ATRESIA. EGBERT H. FELL, A. BENJAMIN M. GASUL, CARL B. DAVIS JR., and RAUL CASAS, Arch. Surg. **59**:445 (Sept.) 1949.

Congenital tricuspid atresia is rare. Three infants with severe increasing cyanosis due to congenital tricuspid atresia were successfully operated on by the Potts-Smith procedure. Severe cyanosis occurring in infancy associated with an enlargement of the left ventricle, diminution of the right ventricle, and a left axis deviation as evidenced by the electrocardiogram are indicative of a tricuspid atresia. The life expectancy is less than one year. The group of patients with this defect is small, but if the diagnostic criteria are kept in mind, relief is possible through surgical measures if there are no other congenital abnormalities to contraindicate an operative procedure.

KAISER, Rochester, N. Y.

COARCTATION OF THE AORTA IN EARLY INFANCY. MARTIN M. CALODNEY and MERL J. CARSON, J. Pediat. **37**:46 (July) 1950.

Calodney and Carson say that coarctation of the aorta may be one of the commonest causes of cardiac failure during the first months of life. Patients with it usually seem normal at birth, but by the age of two weeks 78% show signs of cardiac failure. Infants with coarctation usually have the "infantile," or "preductal," type. However, the "adult," or "postductal," type and combinations of the two types are also seen in infancy. The diagnosis and treatment of this anomaly is discussed in detail.

MACDONALD, Pittsburgh.

DIAGNOSIS OF TRICUSPID ATRESIA OR STENOSIS IN INFANTS: BASED UPON A STUDY OF 10 CASES. BENJAMIN M. GASUL, EGBERT H. FELL, WILLIAM MAVRELIS, and PAUL CASAS, Pediatrics **6**:862 (Dec.) 1950.

The authors have studied 11 cases of tricuspid atresia and stenosis in infants during the past four years. Since the most important therapeutic measure is surgery, the authors classify these cases into two types: The first type is amenable to surgery because it presents either a stenosis or atresia of the pulmonary artery; in the second type surgery is not indicated because the pulmonary artery is not stenotic or atretic. The clinical, fluoroscopic, roentgenologic, electrocardiographic, and angiocardiographic findings in these two types are discussed.

FROM THE AUTHORS' SUMMARY.

ACUTE INFANTILE GAUCHER'S DISEASE: CASE REPORT. CHARLES LAWRENCE RODGERS, and SANFORD HUGH JACKSON, Pediatrics **7**:53 (Jan.) 1951.

A case history is presented of a 9-mo.-old girl who died after a five-month illness consisting of dysphagia, excess of pharyngeal mucus, nuchal rigidity, opisthotonos, fever, splenomegaly, trismus, and generalized weakness. Postmortem examination revealed typical Gaucher cells in the lungs, thymus, liver, spleen, lymph nodes, intestines, adrenals, and bone marrow. This is a case of the acute infantile variety of Gaucher's disease.

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat, and Ear

PHYSICAL AND ROENTGENOLOGIC FINDINGS IN THE EARLY DIAGNOSIS OF NONOPAQUE FOREIGN BODIES OF THE BRONCHIAL TRACT. A. Q. PENTA, Eye, Ear, Nose & Throat Month. **28**:533 (Nov.) 1949.

Nonopaque foreign bodies in the tracheobronchial tree, particularly in children and infants, present a most troublesome problem in diagnosis, since in many instances they are frequently overlooked as a diagnostic possibility. Adequate history and special attention to the physical and roentgenologic findings are of the utmost importance in the diagnosis of nonopaque foreign bodies. In all children and infants presenting the symptoms of laryngeal stridor, cough, bronchial wheeezing, dyspnea, and elevation of temperature, the possibility of aspirated foreign body should always be strongly considered as a diagnostic possibility. Early bronchoscopic examination is indicated in order to avoid serious pulmonary complications due to obstruction and secondary infection.

JENNES, Waterbury, Conn. [ARCH. OTLARYNG.]

CHRONIC OTITIS MEDIA. F. MCGUCKLIN, J. Laryng. & Otol. **43**:328 (June) 1949.

This report consists of a series of nearly 200 cases of chronic discharging ears. McGucklin noted that long-standing, continuous chronic processes often do not respond to simple drainage or an uncovering operation, as do the relatively early processes. There are two factors, among others, of considerable importance: (1) reservoirs, single or multiple, and (2) irreversible changes in the form of inflammatory or degenerative processes in the lining membrane and adjacent bones. Because of its erosive character and its threat to hearing and balance or to the intracranial structures, chronic otitis media should not be considered benign. Surgical intervention in this type of case should be excisive rather than merely surgery of drainage. This includes attention to the outlying cells, removal of diseased lining tissue, and curretage or polishing of underlying bone. The surgical technics are classified under five main headings, each of which is discussed thoroughly. McGucklin's method consists in a modified endaural approach according to the case at hand. The diseased bone and lining membrane are completed, removed, and the cavity is dried with thrombin and powder, consisting of sulfonamides, urethan, and boric acid. The latter is insufflated into the cavity. Packs are used on the flap, and the first incision is sutured. The patient is permitted to get up in two or three days and the sutures are removed on the fifth day. Brief thiopental sodium (pentothal sodium®) anesthesia is given on the seventh day when the packs are removed.

LEJEUNE and STUART, New Orleans [ARCH. OTOLARYNG.].

MENINGIOMA OF THE SPHENOID RIDGE IN A CHILD. COLLIN S. MACCARTHY and LOUIS J. GOGELA, J. Neurosurg. **2**:182 (March) 1949.

MacCarthy and Gogela report the case of a 12-yr-old boy with a meningioma of the sphenoid ridge. They believe that the patient is the youngest whose case is on record. Proptosis of the left eye was first noted at the age of 5 yr. The tumor was asymptomatic until three months before the patient's admission to the hospital at the age of 12, when he complained of headache, especially severe about the left eye and radiating to the occipital region. The pain progressed in frequency and severity and was accompanied with nausea and vomiting 10 days before his examination. There was protrusion of the left eye with some downward and outward displacement. Visual acuity was decreased to 6/30 in this eye. Roentgenograms of the skull revealed a large mass in the left frontoethmoid region which had eroded the supraorbital ridge, the roof of the orbit, and the greater wing of the sphenoid bone. There was a diffuse opacity of all the paranasal sinuses.

At operation a psammomatous meningioma was found attached to the periosteum of the orbital roof and crista galli. It had involved the greater wing of the sphenoid bone, the crista galli, the orbital plate, and the posterior wall of the frontal sinus. The tumor was removed entirely.

Six months later the patient had had no return of his headaches, nausea, or vomiting. There was slight persistence of a downward and forward displacement of the left globe, but the ocular movements, the fundi, and the visual fields were normal.

TOZER, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

PROGNOSIS IN THE HARD-OF-HEARING CHILD. D. E. STAUNTON WISHART, Laryngoscope **57**:460 (July) 1947.

It is in children that the otologist has the greatest opportunity to restore hearing. Methods of testing hearing have not been standardized. The audiometer will easily test the threshold hearing for pure tones, but it does not test the ability to hear speech. In addition to the pure-tone audiometer, the otologist should have a phonograph audiometer with certain recordings. The instruments must be used correctly or the results will be misleading; proper methods are described. The otologist should do the testing himself, rather than leave it to a trained technician.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

EPISTAXIS. J. H. OGURA and B. H. SENTURIA, Laryngoscope **59**:743 (July) 1949.

Epistaxis is discussed thoroughly and well. Topics included in the discussion are anatomy, causes, site of lesion, age factor, and treatment.

In children all bleeding was observed to come from the anterior septum. As age increased so did the incidence of posterior and lateral bleeding. Submucous elevation controlled persistent bleeding from the anterior septum in many cases.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

RHINOLOGY IN CHILDREN: RÉSUMÉ OF AND COMMENTS ON THE LITERATURE FOR 1948. D. E. S. WISHART, Laryngoscope **59**:929 (Sept.) 1949.

Wishart's excellent review includes such subjects as head colds, complications of sinus disease, allergy, irradiation, physiology, tonsils, and adenoids, tonsillectomy and poliomyelitis, fractures of the nose, surgery, and new growths. The review (and some of the source articles) should be read in full.

HITSCHLER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

DEAFNESS AS IT OCCURS IN VARIOUS AGE GROUPS. C. STEWART NASH, New York J. Med. **49**:2409 (Oct. 15) 1949.

From the department of otolaryngology, University of Rochester School of Medicine and Dentistry, Dr. Nash presented a paper before the New York State Medical Society, at Buffalo, May 6, 1949. He urged early diagnosis, at least during the first or second year, when the deafness is correctable. Early diagnosis is a responsibility of parents, teachers, and nurses but especially of otologists. The Spencer Tracys established the John Tracy Clinic in Los Angeles when an otologist told them that nothing could be done about their son's deafness.

The neglected remediable deafness of today may be the permanent disability of tomorrow. For achieving the diagnosis, every factor must be thoroughly examined: the external meatus, the drum membrane, the ossicular chain, the presence or absence of air in the tympanic cavity, the state of the organ of Corti, the functionability of the auditory nerve, and the capacity of the higher centers (brain and pathways) to interpret sound.

For the congenitally deaf there are now "aids" and educational facilities. For the 2½ to 12-yr.-old children, the tonsils and adenoids must be removed thoroughly, and it must be ascertained that the eustachian tubes are patient after operation. Eustachian-tube deafness is curable. From the age of 12 to 20 osteoporosis and otosclerosis are common, and when the footplate of the stapes becomes fixed, fenestration is to be considered. In the 20 to 40 age period, one must look out for an arthritic or rheumatoid cause. Between the ages of 40 to 60, arteriosclerosis may be responsible. Here vitamin B can be useful. Just why or how vitamin B works is problematic, but its administration does seem to be effective at times.

Irrespective of age groups, one must keep in mind such causes of deafness as toxins formed in the body through infectious diseases. The toxins of such conditions as measles, scarlet fever, pneumonia, mumps, encephalitis, and meningitis are effective in producing pathologic changes in any of the sense organs. These are perhaps the most vicious causes of deafness. The resultant deafness is always dependent on nerve degeneration and is, therefore, irreversible.

Drug deafness has long been known. Prolonged administration of quinine has caused deafness, usually accompanied with ringing in the ears. Whether the newer analogous agents used

in malaria, such as quinacrine hydrochloride, will have a similar effect has not yet been determined, or, at least, has not been generally reported.

Recently, deafness after administration of streptomycin has been described. It is severe and seems to be permanent. However, it may be the price which must be paid for saving a life.

In the discussion, Dr. Greydon Gill Boyd, of New York, said that "for the acoustically handicapped, audiology is the avenue to learning, earning, and discerning."

I. W. Voorhees, New York [Arch. Otolaryng.].

The Management of Ear Problems in Children. Marvin F. Jones, New York J. Med. **49**:2825 (Dec. 1) 1949.

Jones urges that the partially deafened child be examined for nasopharyngeal growths regardless of a previous adenoidectomy, for, while thorough removal of tonsils usually eliminates recurrence, this is not always true of adenoids, which have a tendency to recur, no matter how thoroughly they were excised. He insists on the use of the nasopharyngoscope but realizes that many children will defeat this purposeful examination. The author notes that there are fewer cases of acute and chronic suppurating ears in children now than formerly, and he ascribes this, not to the current use of antibiotics exclusively, but to good surgery, the clearing up of sinusitis, and better attention to malnutrition and allergic manifestations. Concerning the use of radium, the author is not overly enthusiastic, although he recognizes the value of positive results reported from dependable sources. Sinusitis is frequently associated with infected tonsils and adenoids. It can often be successfully treated without surgery of the sinuses. Seven "run of the mill" case reports are included in which successful management restored a child's hearing. It is important not to place a child aside in a "deaf class" but to encourage association with normal children, save, perhaps, in the case of the congenitally deafened child. With such a child much can be accomplished by individual instruction, patience, and fortitude. Often he can become self-supporting and is not introverted because of his misfortune. Jones concludes that the otologist will not get the best results unless he does the work himself.

I. W. Voorhees, New York [A. M. A. Arch. Otolaryng.].

The Hard of Hearing Program in the Public Schools of Pennsylvania. James E. Landis, Pennsylvania M. J. **52**:1380 (Sept.) 1949.

The Committee on the Conservation of Hearing for the state of Pennsylvania reports that there are approximately 45,000 school children in the state with various degrees of deafness. This means that from one to three children in every schoolroom have trouble with their hearing, or from 3 to 4% of the school children in the state.

Hearing tests alone do not constitute an adequate conservation of hearing program. The tests reveal identity of the children in need of special medical and educational attention. Hearing programs must have the cooperation of local physicians, audiometric technicians, and local school personnel.

The public must be educated to the fact that neglect and improper care will create a handicap in the pupil, both from an educational and from a psychologic standpoint.

The State Legislature through the Department of Public Health, has approved medical examinations by a certified otologist on children showing a loss of 20 db. or more in two or more frequencies, and it is hoped to have all the cases classified after two years of examinations. This is a decided step forward in determining the cause of early deafness.

From the Author's Summary.

Dermoid Cysts of the Nose. A. D. Davis and R. E. Berner, Plast. & Reconstruct. Surg. **3**:345 (May) 1948.

Many cases of dermoid cysts of the nose have been recorded in the literature since 1933. The otolaryngologists are first confronted with the treatment of this type of cyst. The embryologic and anatomic discussion is complete and accompanied with several photographs of the three unusual cases presented. The authors summarize their article: Dermoid cysts of the nose are not a rarity; approximately 50 cases have been recorded in medical literature. The dermoid cysts

are of special interest because of their embryonic origin. The plastic surgeon should be aware of their origin and possible ramifications. In suspected cases the diagnostic aids of roentgen rays and instillation of iodized oil U. S. P. should be utilized to determine the extent and depth of the cyst. They may present a complex picture and are frequently not recognized or adequately removed.

SELTZER, Philadelphia [ARCH. OTOLARYNG.].

SURGICAL TREATMENT OF THE BIFID NOSE. J. P. WEBSTER and E. G. DEMING, Plast. & Reconstruct. Surg. **6**:1 (July) 1950.

Webster and Deming discuss in detail the surgical treatment of bifid nose. The summary of the entire article presents an excellent and well-described procedure. A general analysis of bifid nose and concomitant deformities is made on the basis of 10 patients who came under their care in the clinic during the past 18 yr. These 10 cases are presented, together with the experience gained from the eight patients who underwent surgery. Procedures for the correction of this deformity are described together with various modifications. Other authors have been of the opinion that the problem of hypertelorism was insurmountable. However, the importance of reduction in the wide spacing of the component parts of the face adjacent to the eyes to produce an optical ilusion minimizing the apeparance of hypertelorism was realized and is here presented as a fundamental factor in giving patients with either true or suggested hypertelorism as normal an appearance as possible. This is accomplished by the excision of tissue in the midline of the forehead and bridge of the nose with closure after wide lateral undermining, possibly supplemented with Y-V plastic procedures of the eyebrows. The wide nose is narrowed by fracture of the nasal processes with medical displacement. Further elimination of epicanthal folds and narrowing of the space between the inner canthi is accomplished by the use of free grafts of cartilage or excess nasal bone to build up the bridge. Because of the frequent development of personality complexes, surgical correction of the bifid nose should be started at an early age. There are 34 excellent illustrations of 10 cases.

SELTZER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

VOMITING AFTER TONSILLECTOMIES. L. KOLESZAR, Pract. oto-rhino-laryng. **11**:277, 1949.

The author discusses postoperative vomiting in a series of 200 tonsillectomies. He states the belief that this vomiting is produced by a period of acidosis, and he has successfully neutralized such patients with intravenous injection of 10 cc. of 10% dextrose solution to which he adds 20 units of insulin.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

MALIGNANT NECROTIC TRACHEOBRONCHITIS. G. CALICETI, Oto-rino-laring. ital. **15**:371, 1947.

The American and French authors report numerous cases of laryngotracheobronchitis, but only in the German literature has the author found such a thing as "trachitis necrotica," of a description similar to the case encountered by himself. A 9-yr.-old girl, hospitalized with signs of laryngotracheobronchitis, was tracheotomized immediately and died three hours later. The whole inner wall of the trachea was found covered with macerated, necrotic epithelium, microbic masses (cocci and gram-positive diphtheroids), and edema of the corion. There were no fibrin or leucocytes; an intact cartilage was present.

MELUCCI, Philadelphia [ARCH. OTOLARYNG.].

ACUTE FULMINATING OSTEOMYELITIS OF THE FRONTAL SINUS COMPLICATED BY MENINGITIS AND CEREBRAL ABSCESS. RUÁL VELASCO L., Rev. otorrinolaring. **9**:57 (June) 1949.

The author presents an interesting case of a 17-yr.-old young man in whom an acute frontal sinusitis developed after he had been swimming while he had an acute upper respiratory infection. Within four days after the onset of his frontal symptoms, evidences of an osteomyelitis and meningitis appeared. Operation revealed a bilateral purulent frontal sinusitis with a frank osteomyelitis. There was an extensive involvement of the left half of the frontal bone and part of

the parietal bone, with frank necrosis and a presence of a subdural abscess. In spite of operation, and massive doses of penicillin, the temperature remained high, and within two days symptoms of a cerebral abscess were presented.

Although he was kept under observation for about three weeks, the symptoms still continued. The operative field was reviewed and an abscess found in the posterior part of the frontal lobe; 60 cc. of pus was removed. A week later another abscess in the parietal region was tapped, with the removal of 40 cc. of fluid. After the drainage of the second abscess, the patient made an uneventful recovery.

The author points out certain important facts: The infection was initiated by the patient's bathing in a swimming pool while having an acute upper respiratory infection. Staphylococcus albus was the infecting organism. A marked amount of spongy tissue was present throughout the bones of the skull. He also noted the surprising facts that the blood count and the spinal fluid were normal after the first operation although two cerebral abscesses developed subsequently and, lastly, that massive doses of sulfadiazine, penicillin, and streptomycin were unable to prevent the development and spread of osteomyelitis and subsequently the brain abscesses but did prove effective in the control of meningitis.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

IRRADIATION OF ADENOID TISSUE. J. M. LEMEE and L. PORTE, Acta oto-rhino-laryng. belg. **3**:378, 1949.

Radium treatment of enlarged adenoid tissue in the nasopharynx should not be considered as a panacea. One should look for and deal with the many causes of lymphoid hyperplasia, in addition to irradiating the tumor itself. These causes are the following: (1) chronic sinusitis, (2) nasal allergy, (3) status thymicolymphaticus, and (4) hereditary syphilis and tuberculosis.

In particular, any suppuration originating in the nasal sinuses should be cleared by the displacement method and a roentgenogram of the nasal sinuses made before irradiation of the nasopharynx is performed. The authors use Crowes' method of three treatments separated by two-week intervals, a 50 mg. radium applicator made of Monel metal being applied for 12 min. For children smaller doses should be used; the writers apply the radium one minute for each year of age up to 10; a treatment is given every two weeks. This is because a child's nasopharynx is smaller than an adult's and more sensitive to radiation; moreover, the pituitary gland is much closer to the pharyngeal wall than it is in an adult.

HERSON, Chicago [A. M. A. ARCH. OTOLARYNG.].

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

HEMANGIOMAS OF THE MOUTH. FREDERICK A. FIGI, Ann. Otol. Rhin. & Laryng. **56**:853 (Dec.) 1947.

Hemangiomas are often encountered about the face and neck and may extend into the oral cavity, but hemangiomas limited to the interior of the mouth are rare. These tumors are congenital or appear shortly after birth and in general are divided into capillary and cavernous types, both of which are subdivided. Capillary hemangiomas include the port-wine stain, or nevus flammeus, and the strawberry birthmark of the hemangioma simplex; the former may involve the oral mucosa, but the latter has not been seen by the author. Cavernous hemangiomas often occur in adults as small, varixlike masses at the vermilion border of the lips or in the oral mucosa and may be due to trauma. The congenital forms may be large and cause enlargement and distortion of the involved parts. Closely allied to the cavernous type are the plexiform or racemose hemangiomas, but these are less common and are probably cavernous hemangiomas with single or multiple arteriovenous fistulas. They are expansile, pulsating tumors, which may be diffuse and of considerable extent. They can be only partially obliterated by pressure and become tenser than simple cavernous angiomas when the patient strains or the part is dependent. A bruit is usually audible and a thrill frequently palpable. Because of arterial pressure they are firmer than the simple cavernous hemangiomas and tend to progress. Phleboliths are commonly found in cavernous hemangiomas in adults and vary from rather soft consistency to calcareous hardness and range in size from 2 or 3 mm. to more than 1 cm.

Since the vessels composing the strawberry type of capillary hemangiomas are lined with the infantile form of endothelium, they respond well to irradiation. The author prefers this method to excision or the use of solid carbon dioxide and says that it produces a minimum of scarring. Port-wine stains are largely lined with a flattened, adult type of cell, and the cells give little or no response to irradiation. If radiation is used, many of these later show malignant degeneration. Cosmetics are best used to hide the stain. Sometimes excision with skin grafting is used. A nevus flammeus of the lip associated with a cavernous hemangioma which is causing enlargement and deformity should be controlled by electrocoagulation and by the injection of a sclerosing solution before excision and skin grafting.

In general, irradiation is the treatment of choice for strawberry birthmarks and cavernous hemangiomas in infants and small children. In adults, cavernous lesions are more effectively treated with electrocoagulation and injections of boiling water or sclerosing agents. Well-circumscribed hemangiomas often are best excised. Plexiform or racemose hemangiomas usually require ligation of the afferent vessels, in addition to the measures employed in treating cavernous hemangiomas.

MILLER, Philadelphia [ARCH. OTOLARYNG.].

APPENDICEAL ABSCESS IN A FOUR MONTH OLD INFANT. MAXWELL P. BOROVSKY, Illinois M. J. **98**:307 (Nov.) 1950.

A case of a walled-off appendicular abscess in a 4-mo.-old infant is reported. Conservative management was carried out for five weeks after the onset, when incision and drainage became necessary. Five months later surgery revealed the appendix completely sloughed off and part of an omental cyst.

FROM THE AUTHOR'S SUMMARY.

THE MANAGEMENT OF LYE BURNS OF THE ESOPHAGUS. GILBERT E. FISHER and JAMES J. HICKS, South. M. J. **41**:591 (July) 1948.

Fisher and Hicks report having treated 34 patients for lye burns of the esophagus in the past year. Immediately after the patient presents himself in the emergency room for treatment, he is given a mouth wash of a weak solution of acetic acid and is asked to swallow a small amount of it. This treatment is followed by a mouth wash and the swallowing of a bland oil. A nasal tube is then passed into the stomach, and the stomach is washed thoroughly with diluted acetic acid and water. A bland oil is then instilled into the stomach. The tube is left in place for three days, and a high calory, high vitamin diet is administered. On the fourth day the patient is examined with an esophagoscope. If only small areas of the esophagus are burned, daily dilatations are begun with a rubber bougie. The size of the bougie varies with the size and age of the patient. After 10 or 12 dilatations these patients usually need no further treatment. In the severer cases in which burns occur at different levels and involve the entire circumference of the esophagus, daily dilatations are done using the E. N. Broyles esophageal dilatators as tolerated; they vary in size from 12 to 32 F. If the dilatation can be carried out successfully at the beginning, the patient is at once directed to remain on a liquid or semisolid diet. These patients must be seen daily for at least two weeks to see that they are receiving sufficient food and fluids and to see that swallowing is not impaired.

Greatest difficulty occurs in those patients who are not seen until several days after receiving the burn. In these patients esophagoscopy must be carried out at once to determine the extent of mucosal damage. In severe burns involving the hypopharynx and the upper one-third of the esophagus, dilatation is very difficult. These patients should have dilatation treatment daily or every other day, with the largest dilatator possible, but with care not to overstretch the injured tissue. If after a few days a 24 F. dilatator can be tolerated and frequent dilatations are maintained for a month or longer, the interval may be diminished to twice weekly, and this should be continued over a much longer time. If the dilatations are discontinued, complete stenosis may follow. When this occurs, an intrathoracic esophagogastrostomy may have to be done. If the stenosis is not complete, weekly or biweekly dilatations will usually suffice. These patients may have some difficulty during periods of acute infection of the upper respiratory tract. Seven illustrative cases are presented.

SINGLETON, Dallas, Texas [A. M. A. ARCH. OTOLARYNG.].

SMALL TRIANGULAR FLAP OPERATION FOR THE PRIMARY REPAIR OF CLEFT LIPS. J. B. BROWN and F. MCDOWELL, Plast. & Reconstruct. Surg. **5**:892 (May) 1950.

Brown and McDowell describe their method for repair of single-cleft lips, by which a triangular flap is turned down from the margin of the ala into the defect in the lip. The method permits the use of thicker vermilion tissue on the alar side, and in this way the full thickness on the other side of the cleft is matched, with the result of a lip of more normal contour. Full details for the operative procedure are given, and a number of excellent photographs add to the clarity of the description.

SELTZER, Philadelphia [A. M. A. ARCH. OTOLARYNG.].

PERFORATION OF THE ESOPHAGUS BY FOREIGN BODIES, AND EMERGENCY TREATMENT. J. P. TAILLENS, Pract. oto-rhino-laryng. **10**:215, 1948.

Taillens discusses the dangers of esophageal perforation by foreign bodies, the principle danger being that of a mediastinitis, which is almost invariably fatal. This complication is not due to trauma, per se, but to secondary infection carried in from the digestive tract. He advises an immediate emergency gastrostomy, after the extraction of the foreign body by the esophagoscope.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

CONGENITAL ATRESIA OF OESOPHAGUS. R. H. R. BELSEY and C. P. DONNISON, Brit. M. J. **2**:324 (Aug. 5) 1950.

In 1947 Franklin, in *Lancet*, mentioned that congenital atresia of the esophagus occurred in 1 in 2,500 births. Belsey and Donnison, however, report that in their experience the incidence is much greater than that, being about 1 in 800 deliveries. They state that a number of cases are not diagnosed and that deaths which are due to this condition are attributed to other causes; it is their belief that this condition is even commoner than the above-mentioned figure.

The diagnosis is easy to make if the condition is suspected, and an early sign is the infant's bringing up large amounts of frothy mucus. It is pointed out that it is important that these children should not be fed by mouth until this condition has been excluded. The diagnosis is easily made by the passage of a rubber catheter into the stomach and can be confirmed by x-ray studies with a contrast medium.

These authors report 10 patients who were treated by operation; five patients survived. The transpleural approach was used in all five of the successfully treated patients. It is also stated by the authors that feeding by mouth can be resumed 24 hr. after operation or earlier and that a gastrostomy appears to be unnecessary in the uncomplicated cases.

BIRDSONG, Charlottesville, Va.

BILATERAL CHOANAL ATRESIA. PHILIP RAINSFORD EVANS and R. J. CANN, Proc. Roy. Soc. Med. **41**:454 (July) 1948.

Three cases of bilateral choanal atresia are reported in three patients, aged 15 weeks, 18 mo., and 15 mo. respectively.

WILLIAMSON, New Orleans.

THREE CASES OF MECKEL'S DIVERTICULUM. L. A. WILSON, Clin. Rep. Adelaide Child. Hosp. **1**:157 (Nov.) 1948.

Three cases of Meckel's diverticulum occurring in a period of a few weeks, all with passage of bright red blood from the rectum as their only symptom, are reported.

MCGUIGAN, Evanston, Ill.

INGESTION OF AN OPEN SAFETY PIN IN AN INFANT. W. A. CARTER, Clin. Rep. Adelaide Child. Hosp. **1**:292 (Nov.) 1948.

A 6-mo.-old infant snatched at and swallowed a 1-in. (0.5 cm.), open safety pin. The pin was passed by rectum three days later. Conservative management, with x-ray observation, is recommended in these cases.

MCGUIGAN, Evanston, Ill.

CARDIOSPASM IN A CHILD. ASITA LAL SOM, Indian J. Pediat. **15**:69 (April) 1948.

A case of cardiospasm in a 10-mo.-old child is reported. The author suggests dilatation by a thick rubber catheter.

McGUIGAN, Evanston, Ill.

HEPATIC CIRRHOSIS OF INFANTS AND CHILDREN. G. K. GAN, Indian J. Pediat. **17**:67 123 (July) 1950.

Sixty cases of cirrhosis are analyzed. Gan suggests that the signs and symptoms indicate a possible relation between the undeveloped reticuloendothelial system of the unborn child and the development of cirrhosis later. There may be some maternal dietetic factor responsible, possibly a protein deficiency.

McGUIGAN, Evanston, Ill.

A COMPARATIVE HISTOPATHOLOGICAL STUDY OF "INFANTILE CIRRHOSIS OF THE LIVER" OF INDIA WITH CIRRHOSIS OF THE LIVER IN INFANTS IN EDINBURGH. A. EDWIN SUNDARESON, J. Indian M. A. **18**:1 (Oct.) 1948.

Comparative studies showed essentially similar findings in cases from India and Edinburgh. It is suggested that a protective factor is absent from the diet of patients with this disease, its absence permitting a second factor, probably a toxin absorbed from the intestinal tract, to cause degenerative changes in the liver.

McGUIGAN, Evanston, Ill.

MANAGEMENT OF ACUTE DIARRHOEAS IN CHILDREN. N. G. MOJUMDAR, J. Indian M. A. **20**: 31 (Oct.) 1950.

The various treatments used in acute diarrheas are outlined. Attention is called to the differences in the extracellular fluid content of adults and children and other factors influencing dehydration. Treatments and physiological discussions are modern and well presented.

McGUIGAN, Evanston, Ill.

THE SURGICAL TREATMENT OF CICATRICIAL STENOSIS OF THE ESOPHAGUS. ROLDOFO REDI. Bull. schweiz. Akad. med. Wissensch. **5**:114 (May) 1949.

The author discusses the subject of stenosis of the esophagus. He states that of every 100 cases of stenosis, 92 are due to burns by chemical agents, 2 to tuberculosis, 2 to nonspecific esophagitis, 1 to ulcer, and 3 to miscellaneous causes. He omits the question of carcinoma of the esophagus, which must be treated separately.

First he recalls that the most effective method for combating stenosis of the esophagus from burn scars is the immediate treatment of the lesion. This idea is relatively new, if one considers that in 1924 no precautions were taken after burns to preserve the normal caliber of the esophagus.

Next the author mentions the therapy of stenoses which are already present but still incomplete and capable of being dilated by various techniques and special instruments to a diameter wide enough to allow the normal passage of food. Finally the author discusses stenoses which are already established and are inaccessible to all bloodless methods of therapy but which justify surgical intervention.

After an initial period characterized by intrathoracic operations, which were almost invariably unsuccessful, this form of surgery was gradually replaced between 1900 and 1938 by what is known as prethoracic esophagoplasty. This development was brought about by the absence of effective agents against bacteria (today we have at our disposal antibiotics and bacteriostatic agents) and of a suitable method of anesthesia which would ensure a sufficiently long narcosis and, according to the case, a collapse or a distention of the lung (pressure anesthesia).

Thanks to the agents which have recently been placed at the disposal of the surgeon (pressure anesthesia, bacteriostatic agents, antibiotics), not only has surgery of the thoracic part of the esophagus been able to reestablish its place but it is even assured a position of the first importance, enhanced by the introduction of numerous techniques, some of which are very audacious. This new surgery, which is largely used with other criteria and other indications, even in

cancerous conditions, has given excellent results. The author concluded with the hope that in this field, as in other branches of surgical practice, larger and larger numbers of operations and observations will result in an increasing proportion of success.

FROM THE AUTHOR'S SUMMARY.

THE APPEARANCE OF URIC ACID IN THE CEREBROSPINAL FLUID IN INFANTS WITH TOXICOSIS. VON P. FERENCZ and D. BODA, Ann. pædiat. **175**:459 (Dec.) 1950.

In the course of investigations carried out on the cerebrospinal fluid of children with toxic gastroenteritis, Ferencz and Boda observed an acceleration of the reduction of permanganate such as had been found in earlier examinations only in cases of severe meningitis, while other changes in the fluid which are characteristic of meningitis, e. g. a pronounced increase of the protein content and the number of cells, were absent. The decisive factor for the reduction proved to be uric acid, the presence of which could be shown in the fluid in quantities which represented a multiple of the physiological values. The authors found, however, that the pathologically increased uric-acid content does not correspond to a proportionate part of the noncoagulable protein.

FROM THE AUTHORS' SUMMARY.

RIGA-FEDE DISEASE. S. SZÜCS, Helvet. paediat. acta **3**:477 (Dec.) 1948.

Granuloma of the frenulum linguae in children (Riga-Fede disease), which is most frequently encountered in Southern Italy and Japan, occurs less frequently in other countries. Purely mechanical causes, such as prolonged breast feeding and the loping inward and the sharp and sawlike edges of the lower middle incisors, play a considerable part. Hereditary and infectious factors are of little importance. The clinical course and histological findings, as also eosinophilia, conform to previous accounts of the disease. The blood picture shows a slight increase in immature forms.

FROM THE AUTHOR'S SUMMARY.

PHYSIOLOGY AND FUNCTIONAL TESTING OF LIVER. K. FELIX, Schweiz. med. Wchnschr. **78**:1165 (Dec. 4) 1948.

The paper deals mainly with the use of oxyphenylpyruvic acid for testing liver function. The substance is available commercially under the name "test acid." It is decomposed solely by the liver, and a person with healthy liver decomposes readily all of a 5-gm. dose.

For the test, 2 grains (0.13 gm.) is given by mouth, and its excretion in the urine is determined. An excretion of more than 8% (160 mg.) indicates an injury to the oxidative capacity of the liver. In cases of cirrhosis all may be excreted. Results of the test need not run parallel with the mucic acid test (for galactose) or with the Takata-Ara test, although in cases in which reactions to these tests were positive, an abnormally high excretion of the test acid was noted. But an increased excretion also occurred when the other two tests showed negative results. In cases of epidemic hepatitis the excretion was usually only slightly, if at all, abnormal during the first days. Then it became abnormal, and returned to normal on recovery. In some cases an increased excretion persisted for months. In cases of hepatocellular jaundice an increased excretion occurs, and a greater one occurs in cases of obstructive jaundice. In a case of hemolytic icterus, the results were negative, becoming positive after the removal of the spleen. Severe purulent infections in wounded soldiers led to an increase in the excretion of the test acid, particularly when the pus was not discharged freely. In cases of gas infection there was also increased excretion. When amputation was done promptly, the result was again normal. Inhalation of trimetrotoluene by workers in ammunition factories produced, in the majority of those tested, a definitely increased excretion.

Adding neoarsphenamine or quinacrine hydrochloride to minced liver interfered with the decomposition of the test acid, and so did addition of dinitrophenols. Minced liver taken from rats treated with substances such as trinitrotoluene, quinacrine hydrochloride, neoarsphenamine, and others oxidized only a little of it. Patients with hyperthyroidism showed increased excretion. By certain psychotic patients decidedly abnormal amounts were excreted. It is important that no cheese is consumed by the patient to be tested.

AMBERG, Rochester, Minn.

LIVER SPECIFICITY OF SOME PROTEIN FLOCCULATION REACTIONS. ULRICH P. FREY, Schweiz. med. Wchnschr. **79**:492 (June 4) 1949.

The author starts with the conception that a mucic acid test (for galactose) properly conducted can indicate with greatest certainty damage of the liver parenchyma. Protein flocculation tests, such as the Takata-Ara and the cadmium, the cephalin-cholesterol, and the thymol turbidity, were therefore compared with the mucic acid test. It is concluded that none of these tests is a specific liver function test.

AMBERG, Rochester, Minn.

THERAPY OF APPENDICAL MESARAIC THROMBOPHLEBITIS WITH EMETINE HYDROCHLORIDE. EDUARD MELCHIOR, Schweiz. med. Wchnschr. **79**:673 (July 23) 1949.

Emetine hydrochloride is given subcutaneously. For children a minimal dose of 0.02 gm. daily is recommended until a total dosage of 0.4 or 0.5 gm. is reached. It is also given in severe infections, including those of the biliary tract. The effect is illustrated on three patients. Two had mesaraic thrombophlebitis secondary to acute appendicitis. The third had apparently primary thrombophlebitic appendicitis. One of the first two patients was an 11-yr.-old boy. In this case an insufficient course of treatment had been unsuccessful. The condition became desperate but yielded to a dosage of emetine hydrochloride of 0.02 gm. twice daily up to 0.6 gm. total. It is pointed out that this complication, characterized by shaking chills, is usually fatal. Occasionally, a ligature of more proximal veins can be successful, but in the cases mentioned it could no longer be done.

AMBERG, Rochester, Minn.

THE LIMITS OF THE EFFICACY OF TREATMENT WITH SULFAGUANIDINE IN ACUTE ENTERITIS AND DYSENTERIFORM ENTERITIS IN EARLY CHILDHOOD. GIOVANNI BOI, Ann. ital. pediat. **1**:103 (Dec.) 1948.

The author, after a short review of the main cause of acute disease of the digestive tract of the child and of the therapeutic procedures followed previously, reports the results obtained by him in sulfaguanidine treatment of patients with acute gastroenteritis and dysenteriform enteritis.

In both groups the employment of sulfaguanidine, whether in a massive dose or in fractional doses, has proved to be very efficacious, with recoveries up to 86%, especially if associated with use of autovaccines. The author advances the opinion that the drug acts indirectly through bacteriostatic and antitoxic action.

FROM THE AUTHOR'S SUMMARY.

CLINICAL-ANATOMICOPATHOLOGICAL STUDY OF VON GIERKE'S DISEASE. A. CHIEFFI and L. NASSI, Riv. clin. pediat. **46**:631 (Oct.) 1948.

The authors report five cases of glycogenosis, two with clinical diagnosis and anatomicohistological confirmation, two in which the patients died on the first day of admission that were diagnosed only after necropsy, and one with clinical diagnosis and biochemical findings characteristic of the disease.

The authors describe the clinical and humoral symptoms of each patient and remark that a sufficiently exact diagnosis can be made in cases with typical symptomatology. Contrary to the assertion of some authors, they affirm that biopsy is not necessary for diagnosis, in these cases, although it is indispensable in atypical cases. One patient with icteric manifestations is mentioned.

The anatomicohistological findings in three patients, the characteristic alterations of the liver, and the lesions of some endocrine gland (hypophysis, thymus, adrenals, pancreas) are described. The problem of pathogenesis is amply discussed, and the authors are inclined to believe in an alteration of the endocrine system which concerns first the diencephalon-hypophysis system and second the gland of internal secretion (thymus, pancreas).

The authors confirm the findings of a preceding paper on the hyperglycemic action of the liposoluble thymus extracts in glycogenosis. The favorable results obtained with these extracts in some manifestations of the disease, such as in the last case observed, are brought to attention.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF INFANTILE DIARRHEAS WITH MIXTURES OF SULFONAMIDES. A. MONTERO RODRIGUEZ, Acta pediat. españ. **92**:943 (Aug.) 1950.

Rodriguez discusses diarrhea as a symptom of bacterial and virus infections and as secondary to diseases. However, he believes nutrition and lowered immunity are the bases for most cases. Proper feeding from birth would prevent many cases of inanition, which so often accompanies infantile diarrhea, and would render many immune to the frequent etiologically ill-defined diarrheas.

Besides the usual treatment with saline and plasma, he found a mixture of sulfadiazine, sulfathiazole and urea very rapid and effective for treatment in cases in which the disease was resistant to sulfonamides used singly. He quotes Hadler and McClain in saying that the area reinforces the action of the sulfonamides and inhibits in part the action of paraaminobenzoic acid.

Included are the case histories of the five severest instances of diarrhea in which treatment was by this method. The dose used was 0.20 Gm. per kilogram of body weight a day. Feeding, intravenous and subcutaneous saline and glucose solutions were employed, and it was found that the children tolerated purees and amino acids given by mouth quite well shortly after the start of the treatment.

ALLEN, Santa Fe, N. Mex.

DIARRHEA IN CHILDHOOD. FEDERICO GOMEZ, Bol. méd. Hosp. inf., México **6**:1 (Feb.) 1949.

The author gives an exhaustive description of diarrheas, evaluating the principles on which so far the classifications of diarrheas have been based. Ever since Hippocrates, he says, diarrheas have been classed as diseases, although they are only a symptom of disease. All the authors who have dealt with this problem have fallen into the same error. The author analyzes the better known classifications of diarrheas and finds them all wanting. He offers a classification which is simple and easy to remember. It comprises three gorups: (1) noninfectious diarrheas, (2) diarrheas caused by enteral infections and (3) diarrheas caused by parenteral infections. The author lists all diarrheas under these and gives reasons for their placements, but he says that it should be kept in mind that diarrhea is a symptom and not a clinical entity. Therefore, he invites studious workers to collaborate in the revision of the material concerning diarrheas.

FROM THE AUTHOR'S SUMMARY.

A CASE OF PARTIAL INTESTINAL INCLUSION FROM PATHOLOGIC CHANGE IN THE GALLBLADDER. CARLOS SARIÑANA, Bol. méd. Hosp. inf., México **6**:60 (Feb.) 1949.

A 4 year old girl was admitted with a tentative diagnosis of intussusception. At the operation it was found that the mass that had been felt on the right hypochondrium was the gallbladder enormously dilated, which was compressing the hepatic angle of the colon, thus simulating an intussusception and in this manner preventing the free passage of the barium meal. The gallbladder was shaped like a banana, measuring about 20 cm. in length by 5 cm. in diameter. A paracentesis was done, and about 60 cc. of a dark green liquid was removed; then, 100,000 units of penicillin were injected within the cavity; after this the gallbladder was sutured, and the abdominal cavity was closed. The postoperative course was uneventful.

FROM THE AUTHOR'S SUMMARY.

CHIARI'S DISEASE. RAUL HERNANDEZ, FRANCISCO PARADA, DAVID NAVARRO and ALBERTO GUZMAN, Rev. chilena Pediat. **19**:491 (June) 1948.

The clinical and pathological history is given of a child aged 18 months. The pathologic investigation revealed the existence of extensive thrombosis of the hepatic veins, affecting even the smaller ones. This thrombosis must be considered secondary to a perihepatitis whose cause it was impossible to determine. The child died three months after the onset with jaundice and coma caused by hepatic insufficiency.

FROM THE AUTHORS' SUMMARY.

CAUSTIC STENOSIS OF THE ESOPHAGUS. AUGUSTO LATORE AGUERO, Rev. otorrhinolaring. **7**:81 (Sept.) 1947.

Caustic esophagitis is a frequent occurrence in Chile and is a symptom of a disease that represents one of the most serious social problems, namely, alcoholism. Most of the patients

treated were alcoholic addicts, and the substances used most frequently were hydrochloric acid and sodium hydroxide. The author has treated 41 patients within the past four years. His method was usually that of early dilatation with mercury bougies, starting either on the fifth or on the sixth day after the onset of the condition. Of the group of 41 patients, 11 died and 14 had to have a gastrotomy performed; in 8 patients pulmonary tuberculosis developed. The author is of the opinion that prognosis depends on the immediate institution of emergency treatment, proper dilation, and the maintenance of a diet sufficiently rich in proteins to maintain body weight.

PERSKY, Philadelphia [ARCH. OTOLARYNG.].

OBSERVATIONS ON THE INFLUENCE OF FOLIC ACID ON THE COURSE OF CELIAC DISEASE. R. FILSINGER and K. H. KIMBEL, Arch. Kinderh. **140**:98, 1950.

The authors describe two cases of celiac disease; the patients were 16 months and 4 years respectively. They report the favorable influence of folic acid treatment on weight, glucose tolerance and psychic reactions. The folic acid was at first given intravenously and then orally.

GOTTSTEIN, Chicago.

PAROTITIS EPIDEMICA CHRONICA. K. SCHOTT, Med. Klin. **44**:1410 (Nov. 4) 1949.

In several Russian war prisoners' camps a number of patients were taken ill with a fever usually lasting about two weeks but sometimes for weeks and months. All had a swelling of one or both parotid glands, sometimes with participation of the submaxillar and sublingual glands. Often sore throat was present in the initial stage. Double-sided orchitis could occur and possibly pancreatitis or meningoencephalitis. In some cases the picture repeated itself four to eight months after complete recovery. Some of the patients gave a history of previous mumps.

AMBERG, Rochester, Minn.

RELATION OF RHESUS SYSTEM AND DYSPORIA ENTEROBRONCHOPANCREATICA CONGENITA FAMILIARIS (GLANZMANN). HERBERT BINDEWALD, Med. Klin. **36**:1137 (Sept. 8) 1950.

Dysporia enterobronchopancreatica congenita familiaris is the name given by Glanzmann to cystic fibrosis of the pancreas. On the basis of some observations, Glanzmann advanced a hypothesis that Rh-similar antibodies find their way from the mother to the lungs, intestines and pancreas of the fetus, reacting with intracellular antigens and so leading to injuries of the epithelium leading to the production of abnormal secretions which are the cause of the dysporia. Two cases are reported which certainly belong under this classification and another one which probably belongs. In one case Rh incompatibility could be excluded by taking into consideration also the subgroups. In the other two cases there was no evidence of Rh incompatibility, but incompatibility in subgroups could not be excluded with absolute certainty. In the serum of the mothers neither agglutinins nor glutinins were found.

AMBERG, Rochester, Minn.

RESULTS OF THE WEBER-RAMSTEDT OPERATION FOR PYLOROSTENOSIS OF INFANTS. KLAUS PFEIFER, Med. Klin. **36**:1140 (Sept. 8) 1950.

The Weber-Ramstedt operation was performed on 250 patients with pyloric stenosis, with an operative mortality of zero. During the postoperative treatment 17 infants died. Early operative intervention is advocated.

AMBERG, Rochester, Minn.

EFFECT OF SULFAGUANIDINE AND STREPTOMYCIN ON THE INTESTINAL FLORA OF INFANTS WITH INTESTINAL DISTURBANCES. KURT NITSCH and HELMUT ADAMEK, Monatsschr. Kinderh. **98**:21 (Jan.) 1950.

Untreated patients showed a preponderance of saccharose-fermenting Escherichia coli that was not changed within five days by dietary treatment alone. Treatment with sulfaguanidine caused diminution or disappearance of the saccharose-fermenting Esch. coli and of gelatin-liquefying organisms. The greatest action of streptomycin consisted in marked reduction or disappearance of all gram-negative bacteria, Esch. coli being the most resistant organism found.

Studies of duodenal juice revealed more rapid disappearance of organisms when the infant was treated with streptomycin or sulfaguanidine than with diet alone. In some patients no relation between clinical course and stool flora was seen, and parenteral infection should be suspected in such cases.

HARTENSTEIN, Madison, Wis.

FAT RESORPTION IN CONGENITAL CYSTIC FIBROSIS OF THE PANCREAS IN A CHILD AGED SIX MONTHS. IB BOESEN, Acta pædiat. **37**:309, 1949.

The author reports the case history and clinical and laboratory observations for a patient aged 6 months with congenital cystic fibrosis of the pancreas, the diagnosis of which was made clinically and verified at autopsy. A considerable increase in the weight of the extremely emaciated child was achieved by ingestion of food through a permanent stomach tube.

Experiments on fat balance showed that in an experimental period of 72 hours during which the patient received a total of 30.8 Gm. of fat, 13.7 Gm. (44 per cent of the intake) was excreted. It is demonstrated that because of the reduced pancreatic function the patient became undernourished, the deficiency being at least 80 Calories a day on the diet employed. Compared with the values from a normal subject, published by Dorothy Andersen, it is seen that the patient's daily excretion of fat was four times the normal, while the weight of the feces and the percentage of neutral fat contained in them were within normal limits, although very near the upper limit.

FROM THE AUTHOR'S SUMMARY.

FOREIGN BODIES IN THE ESOPHAGUS WITH SYMPTOMS EXCLUSIVELY FROM THE AIR PASSAGES. H. F. FABRITIUS, Acta pædiat. **37**:335, 1949.

The author reports the cases of two children in whom large foreign bodies remained undetected in the esophagus for 2½ and three months respectively, despite repeated examinations. He points out that neither of the patients had noticeable difficulties in swallowing but that they presented almost exclusively symptoms from the respiratory tract. The symptoms were very confusing and thus involved diagnostic difficulties. The author discusses the two cases and, among other things, emphasizes the necessity of roentgenographic studies with contrast medium even for small children.

FROM THE AUTHOR'S SUMMARY.

ENLARGEMENT OF LIVER AND SPLEEN: A STATISTICAL STUDY OF 1,500 CASES IN INFANTS AND CHILDREN. YUNG-EN KAO, Chinese M. J. **66**:260 (May) 1948.

Enlargement of the liver and spleen was assessed by measuring the distance between the costal margins and the lowest poles of these organs. In this manner, 1,500 infants and children with enlargement of these organs were studied. Of these patients 880 showed enlargement of the liver alone; 352 showed enlargement of the liver and spleen, and 268 showed enlargement of the spleen alone. Most cases occurred in the first two years of life.

Of the many diseases responsible for enlargement of the liver, respiratory infections and bronchopneumonia were the most frequent. In spleen enlargement typhoid and malaria were the most frequent causes and in enlargement of both organs pneumonia and syphilis.

MACDONALD, Pittsburgh.

DUODENAL ULCER IN A CHILD OF TWO YEARS: A CASE REPORT. SHAO-CHOW PAN and YIN-TANG HSU, Chinese M. J. **66**:274 (May) 1948.

Duodenal ulcer in children, first reported in 1864, has been reported with increasing frequency in the medical literature. The authors offer the first such report made in China. The patient, a 2-yr.-old boy, first had blood in the stools at the age of 5 mo. At the age of 2 yr. he became acutely ill, vomited coffee-ground material, and passed tarry stools. He died 12 days after the onset of this final illness. At autopsy a large ulcer was found on the anterior wall of the duodenum.

MACDONALD, Pittsburgh.

CONGENITAL OMPHALOCELE. Z. U. ZEE, Chinese M. J. **67**:375 (July) 1949.

Congenital omphalocele occurred twice in 6,620 births at the Margaret Williamson Hospital, Shanghai. Surgical repair, done within a few hours after birth, was successful in both cases.

MACDONALD, Pittsburgh.

Nervous Diseases

THE TOXIC EFFECT OF STREPTOMYCIN ON THE EIGHTH CRANIAL NERVE: HISTOLOGICAL INVESTIGATIONS; A PRELIMINARY REPORT. KARL BERG, Ann. Otol. Rhin. & Laryng. **58**:448 (June) 1949.

In an effort to determine the actual site of the lesion responsible for vestibular dysfunction unassociated with hearing loss in patients receiving streptomycin over prolonged periods, the author administered the drug twice daily in varying amounts to 25 young cats. The total dose in any animal was the equivalent of 156 to 965 gm. in an adult weighing 70 kg. The duration of treatment ranged from 14 to 127 days. Vestibular function was tested regularly by the rotatory test, the postrotatory nystagmus being recorded. Ultimately, nystagmus became extinct, the time required varying according to the total amount of drug administered.

On conclusion of the experiment, all animals except three were killed, and the vestibular ganglion, the basal coil of the cochlea, and the vestibule were studied histologically. Studies on the remaining three animals will form the basis for a further report. Marked degenerative changes in the sensory epithelium of the crista ampullaris, macula utriculi, and macula sacculi were noted in each animal. The organ of Corti was normal in all except one animal, who had received the largest dose of streptomycin (roughly equivalent to 960 gm. in man, over a period of 127 days). In this instance, considerable degeneration of the sensory epithelium in the organ of Corti was found.

Study of the brain and vestibular nuclei showed no definite pathologic changes. Slight changes in the Nissl substance of the ganglion cells were present.

It is concluded that streptomycin affects primarily the sensory epithelium of the labyrinth, with slight secondary changes in the vestibular ganglion.

STEELE, Kansas City, Kan. [ARCH. OTOLARNG.].

PHENURONE IN EPILEPSY. F. A. GIBBS, G. M. EVERETT, and R. K. RICHARDS, Dis. Ner. System **10**:47 (Feb.) 1949.

Phenacemide (phenurone®) has been found greatly to raise the threshold or completely to suppress electric shock and pentylenetetrazole (metrazol®) convulsions in experimental animals and to be of low toxicity. The authors have now tested the drug on 90 patients with epilepsy of different types, all of whom had been resistant to the usual anticonvulsants. Fifty per cent were not significantly bettered, and 50% were rendered seizure-free or were greatly improved, with the actions of the medication about equal against the three major types of attack. The effect on psychomotor epilepsy is impressive because of the relative failure of diphenylhydantoin sodium and trimethadione in treatment of this kind of convulsion. The average dose given was 2.5 gm. a day, and it was learned that if benefit was not derived from 3.5 gm. a day, larger amounts were also ineffective. The drug is tasteless and easily administered in the food for psychotic patients. Because it is rapidly eliminated, divided doses should be evenly distributed over the day. Common side effects were weakness and anorexia, but the most frequent complication was exaggeration of the preexisting personality disturbances which often accompany psychomotor epilepsy. This occurred in 20% of patients, though incidence will, of course, depend on the prevalence of serious emotional imbalance in the specific group under study. In no patient without prior symptoms was a consequential psychiatric disorder precipitated, and a few patients showed improvement in psychologic status. Character difficulties were usually exaggerated only when psychomotor seizures were controlled, though in a few subjects personality disturbances broke out even if seizures continued. It is suggested that the ictal and nonictal components of the syndrome are independent, or even antagonistic. On withdrawal of phenacetemide, attacks recurred promptly and the emotional disorder subsided, though in one patient there was no resumption of seizures and a severe psychotic state developed, which defied electric shock but yielded to subshock insulin therapy, whereupon psychomotor convulsions returned. Insomnia was

present as a side effect in 6% of subjects but was counteracted by phenobarbital or methylphenylethyl hydantoin (mesantoin®), which also seemed to give additional suppression of attacks. In one case hepatic disturbance, with jaundice, was conclusively traced to the use of phenacetemide, and in two others there were evidences of transient renal damage. Only 1% of patients showed a rash, and no effect on the blood was detected in any.

BEATON, Tucson, Ariz. [ARCH. NEUROL. & PSYCHIAT.].

INFLUENZAL MENINGITIS TREATED WITH CHLOROMYCETIN. R. WILLIAM CARABELLE and DONALD D. MITCHELL, J. Pediat. **37**:37 (July) 1950.

A combination of sulfadiazine, streptomycin, and penicillin failed to control influenzal meningitis in a Negro infant. When chloramphenical (chloromycetin®) was added to the therapy and streptomycin administration stopped, the patient promptly recovered. Encouraged by this, the authors treated four more Negro infants with influenzal meningitis, using oral administration of chloramphenicol alone. The dose was 75 mg., or more, per kilogram per 24 hr. All four infants recovered rapidly and without sequelae. The authors think that it would have been wise to supplement the chloramphenicol with another antibiotic, particularly one effective against gram-positive organisms. They believe this because upper respiratory tract symptoms developed in three of their patients despite chloramphenicol administration.

MACDONALD, Pittsburgh.

REPORT OF A CASE OF INFLUENZAL MENINGITIS TREATED WITH POLYMYXIN B (AEROSPORIN). ELIZABETH BRAKELEY, J. Pediat. **37**:42 (July) 1950.

A 3-yr.-old child had influenzal meningitis. She was given streptomycin, penicillin, and sulfadiazine for 36 hr. Then this treatment was stopped, and she was given aerosporin® (polymyxin B) intramuscularly and intrathecally. With this she was given 100 mg. of specific rabbit antiserum. She recovered.

MACDONALD, Pittsburgh.

CEREBRAL BIRTH INJURY IN RETROSPECT. W. DEAN BELNAP, CHARLES F. MCKHANN, and CLAUDE BECK, J. Pediat. **37**:326 (Sept.) 1950.

Most doctors have thought that the majority of serious childhood cerebral abnormalities are caused by hereditary or intrauterine developmental defects. Not so, say these authors. Birth injury, including anoxia, may be a major causative factor in these cerebral abnormalities. Detailed studies of 419 children with mental retardation, convulsive disorders, or cerebral palsy support this view. Behavior disorders without retardation spasticity or convulsions may be due to milder degrees of cerebral birth injury. About 20% of the birth injuries in this study were preventable.

MACDONALD, Pittsburgh.

BRAIN TUMORS IN CHILDREN. LYLE A. FRENCH, Minnesota Med. **31**:867 (Aug.) 1948.

The authors reviews all the cases of brain tumors occurring in children of 16 and younger who were seen at the University of Minnesota Hospitals from June, 1931 to July, 1946. During this period a diagnosis of brain tumor was made on 202 children. The statement is made that there are fairly constant symptoms that occur in children with brain tumors which lead one to suspect this diagnosis. However, roentgenograms of the skull revealed interesting observations. There was evidence of increased intracranial pressure in 80% of children with brain tumors. Abnormal intracranial calcification was visible in roentgenograms in 20% of children with brain tumors and was an accurate indication of the localization of the tumor. Ventriculograms were of localizing value in 78% of the children with brain tumors on whom such studies were performed.

STOESSER, Minneapolis.

SUBDURAL EFFUSIONS COMPLICATING BACTERIAL MENINGITIS. MARGARET H. D. SMITH, RICHARD E. DORMONT, and GEORGE W. PRATHER, Pediatrics **7**:34 (Jan.) 1951.

The authors present 20 cases of subdural effusion occurring in infants under the age of 14 mo. during their convalescence from acute bacterial meningitis due to Hemophilus influenzae type B, Diplococcus pneumoniae, paracolon bacillus, and Pseudomonas aeruginosa.

The incidence of these effusions must be high, since at least 20 of 43 patients with meningitis under the age of 2 yr. had fluid in the subdural space at some time during their hospital stay.

The authors believe that subdural taps should be performed on admission for diagnostic purposes whenever the patient had been treated with antibiotics before coming to the hospital and has no organisms in the spinal fluid at the time he is first seen, as well as for all patients who give evidence of prolonged fever, focal neurologic signs, convulsions, and other signs after meningitis.

The trauma incident to subdural taps is probably not itself responsible for causing subdural effusions, since in most cases fluid was present at the first tap.

The matter of age incidence needs investigation. There is no reason to believe that such effusions are limited to infants. The possible presence of a subdural effusion should be considered in an older patient whose convalescence from meningitis is slow, accompanied with prolonged fever, headaches, and any suggestive focal neurological signs.

The authors' experience, as well as a review of the older literature, indicates that from the confusing clinical entities with such names as subdural hygroma, pashymeningitis, and hemorrhagica interna, one group can be singled out as occurring on the bassis of an underlying infection. Its frequent occurrence in recent years is due to the high survival rate in the bacterial meningitis.

The actual pathogenesis of this lesion; the incidence of loculated fluid; the incidence of "membranes"; the possible influence of different treatment regimens on the occurrence of this syndrome; the possibility suggested by analogy with "pleuropneumonia" that subdural effusions, when infected, may serve as foci for later recurrences of meningitis, and the possible influence of early recognition and treatment of subdural effusions on the ultimate prognosis in meningitis are matters for the future to determine.

FROM THE AUTHORS' SUMMARY.

CONGENITAL VERBAL-AUDITORY AGNOSIA (WORD DEAFNESS). ISAAC W. KARLIN, Pediatrics **7**:60 (Jan.) 1951.

The term congenital verbal auditory agnosia is proposed as a name for congenital word deafness in children. The clinical features that these children present are (*a*) lack of speech or limited speech and (*b*) an ability to hear sounds combined with inability to comprehend words by the auditory route. The defect is apparently in the audito-psychic area, or Wernicke's area.

The unusual case of a child with congenital verbal auditory agnosia is described.

FROM THE AUTHOR'S SUMMARY.

TWO BROTHERS WITH INFANTILISM, SHOWING SOME FEATURES OF PROGERIA, ASSOCIATED WITH MICROCEPHALY, RETINAL DEGENERATION AND INTRACRANIAL CALCIFICATION. HELEN M. M. MACKAY, Proc. Roy. Soc. Med. **41**:349 (June) 1948.

A. P., aged 15, semed normal until about 1 yr. of age. He walked at 2½ yr. J. P., his brother, aged 10 yr., walked at 2½ yr. He had had a tremor since birth. Both attended a school for mentally defective children. The parents were normal, but the mother's step-brother was reported to be mentally deficient although he could earn a living.

Physical examination of A. P. showed him to be of very small stature and to show lumbar lordosis, slightly protuberant abdomen, talipes valgus, tottering gait, and numerous pigmented moles on the head, neck, arms, and legs. He was microcephalic, with prominent ears and sunken eyeballs; the skin of the face was stretched, with some wrinkling, elsewhere normal; the hair was dry and thin. The blood pressure was 115/60; the teeth were irregular. Examination of the central nervous system revealed slightly irregular and very small pupils which reacted very slightly to light and accommodation. The liver and spleen were enlarged, and there were no secondary sex characteristics present. The fundi showed degenerative retinitis and bilateral optic atrophy. Examination of the brother, J. P., gave very similar results. All measurements and data on investigations of both patients accompany the report.

WILLIAMSON, New Orleans.

STURGE-WEBER SYNDROME: CASE REPORT. Y. BARRADA, Y. GUINENA, ABBAS H. HASSAN, and S. ABD-EL NABY, J. Roy. Egyptian M. A. **32**:323 (April) 1949.

A case of Sturge-Weber syndrome in a girl of 18 is reported, with a detailed discussion of the syndrome.

MCGUIGAN, Evanston, Ill.

STREPTOMYCIN TREATMENT OF INFLUENZAL MENINGITIS. A. LEONE, Ann. ital. pediat. **61**:31 (Dec.) 1948.

The author briefly discusses the problem of the present treatment of influenzal meningitis. He stresses that the administration of serum, sulfonamides, penicillin, or various combinations of these drugs usually has been inefficient.

In seven cases recently observed, streptomycin in appropriate doses eradicated the infection in four patients without clinical sequelae; two patients recovered quickly, but had mild hydrocephalus, which was treated with roentgenotherapy. Two patients died on the first and second day of the streptomycin administration.

The author shows the prompt, constant, and decisive effect of streptomycin administration in influenzal meningitis treated in the first stage of the disease.

FROM THE AUTHOR'S SUMMARY.

MENINGITIS DUE TO THE PFEIFFER BACILLUS, RESISTANT TO SULFADIAZINE-PENICILLIN THERAPY. R. FEROLA, Lattante **19**:540 (Sept.) 1948.

An infant of 12 mo. died of influenzal meningitis despite treatment with generous doses of penicillin and sulfadiazine. The use of streptomycin is recommended as a better antibiotic in treating infections due to Hemophilus influenzae (Pfeiffer bacillus).

HIGGINS, Boston.

OBSTETRICAL PARALYSIS INVOLVING ONLY THE LEFT HALF OF THE DIAPHRAGM. G. MAINI, Lattante **20**:161 (March) 1949.

A 40-day-old infant showing periodic spells of cyanosis and dyspnea was found by roentgenogram to have paralysis of the left side of the diaphragm with pushing of the heart to the right side. Relief of the symptoms was obtained after the giving of penicillin to combat a possible infection. The cause of the condition was ascribed to an obstetrical paralysis. When the child was seen again, at the age of 6 mo., regeneration of the phrenic nerve had taken place, and both sides of the diaphragm were functioning.

HIGGINS, Boston.

PROGNOSIS AND TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS. E. ORLANDI, Lattante **20**:223 (April) 1949.

Of 10 patients with influenzal meningitis treated with sulfonamides, nine died. The one patient who recovered was given sulfadiazine; the other patients had been given sulfapyridine or sulfathiazole.

Of four patients who were treated with streptomycin intrathecally and intramuscularly and with sulfadiazine orally, all recovered within 18 days; no residual symptoms were reported.

HIGGINS, Boston.

FAMILIAL CEREBRAL SPASTIC PARALYSIS: STRÜMPELL'S DISEASE. G. FROLA, Pediatria **56**:377 (July) 1948.

Of six living children in one family, in three boys and one girl a progressive spastic paralysis developed, the ages at onset being between 14 mo. and 3 yr. The parents were healthy and knew of no neurological disease in any members of their families. Two of the boys were studied intensively at the pediatric clinic at Bari, but no further data of importance could be obtained to explain the causation of the condition.

HIGGINS, Boston.

NEPHELOMETRY OF SPINAL FLUIDS IN CASES OF PURULENT AND TUBERCULOUS MENINGITIS. C. COMOLLI and E. CLERICI, Pediatria **56**:436 (July) 1948.

The Wunderly-Wurman technique was used in determining nephelometrically the degree of cloudiness produced by adding 0.5 cc. of spinal fluid to 5 cc. of calcium chloride solutions of various concentrations. A definite degree of cloudiness was noted with the fluids of the patients with meningitis which was not found with the fluids of normal persons. The test, however, proved of no value in differentiating the various types of meningitis.

HIGGINS, Boston.

FROIN'S SYNDROME FROM AN INTRAMEDULLARY HEMANGIOMA. A. VISANI and U. GUELI, Pediatria **56**:490 (July) 1948.

A child of 2 mo. had an abnormally small chest; also the chest muscles were weak, and there was loss of pain sensation in the chest area. She had a urinary infection at the same time. A lumbar puncture revealed Froin's syndrome of the spinal fluid, xanthochromia, immediate coagulation, and increased cell count. Postmortem examination revealed a fluid block due to adhesions of the meninges to the spinal cord from the seventh cranial nerve to the fourth thoracic nerve at the site of a hemangioma of the cord.

HIGGINS, Boston.

SUMMER ENCEPHALITIS. K. T. CHEN and H. H. CHANG, Chinese M. J. **66**:409 (Aug.) 1948.

The first encephalitis which was reported in China was seen in 1935. Other cases have been reported since then. The authors observed 47 cases in the summer months from 1943 to 1945. Most of the patients were children under 10 yr. The virus was not identified.

MACDONALD, Pittsburgh.

EPIDEMIC OF ENCEPHALITIS IN CHUNGKING IN THE SUMMER OF 1944. HUAI-CHIEH KAN, Chinese M. J. **66**:419 (Aug.) 1948.

Huai-Chieh Kan reports 28 cases of encephalitis seen in Chungking in July and August, 1944. Most of the cases were in children, and slightly more than half the number of patients were females. The virus was not identified.

MACDONALD, Pittsburgh.

INFLUENZAL MENINGITIS IN INFANTS. YUNG-EN KAO, HUNG-YUAN LI, and CHU-HSUAN LI, Chinese M. J. **67**:371 (July) 1949.

Eight patients, ages 6 to 11 mo., with influenzal meningitis are reported. Three died. The authors list sulfadiazine, streptomycin, and type B Hemophilus influenzae rabbit serum as effective therapeutic agents. Their effectiveness is enhanced when they are used in combination.

MACDONALD, Pittsburgh.

Diseases of Genitourinary Tract

PRIMARY OVARIAN AGENESIS. LEO S. RADWIN, JOSEPH P. MICHELSON, and JEANNE SHORE, J. Pediat. **34**:143 (Feb.) 1949.

Shortness of stature combined with failure of development of secondary sex characteristics and primary amenorrhea may suggest either panhypopituitarism or an ovarian deficiency. The patient with primary ovarian deficiency exhibits the following features: (1) shortness of stature but not dwarfism of panhypopituitarism; (2) presence of axillary and pubic hair, although decreased in amount (this is never found in panhypopituitarism); (3) infantile breasts, uterus, vagina, and labia, not unlike those found in hypopituitary disease; (4) strong, well-nourished appearance unlike that of the frail, easily tired, pituitary dwarf; (5) moderate retardation of skeletal maturation, epiphyseal closure delayed but eventually occurring (in hypopituitary dwarfs epiphyseal union is often delayed indefinitely); (6) increase in follicle-stimulating hormone of the pituitary (in hypopituitary dwarfs this hormone is absent); (7) moderate reduction of 17-ketosteroids in the urine (in hypopituitary dwarfs the urine usually contains very little 17-ketosteroids); (8) increase of sexual hair by estrogenic therapy (not in hypopituitary dwarfs); (9) normal insulin-tolerance and glucose-tolerance reactions (not in hypopituitary dwarfs); (10) diffuse osteoporosis produced by lack of estrogen in ovarian deficiency, and (11) frequent association of other congenital abnormalities, such as webbing of the neck, coarctation of the aorta, ocular changes, and others.

The patient reported on is a 17-yr.-old girl. She has been successfully treated with estrogens supplemented with progesterone.

MACDONALD, Pittsburgh.

TREATMENT OF MIXED TUMORS OF THE KIDNEY IN CHILDHOOD. ROBERT E. GROSS and EDWARD B. D. NEUHAUSER, Pediatrics **6**:843 (Dec.) 1950.

Mixed tumors of the kidney in infancy and childhood can be easily recognized in most instances by simple procedures of physical examination and pyelography. In general, it is not difficult to differentiate between them and other masses which can appear in the upper quadrants of the abdomen. Therapy in all instances should include transabdominal nephrectomy and postoperative roentgen irradiation to the area. Whether preoperative irradiation has any advantage other than reducing the size of the mass and facilitating its operative removal is still unproved in the authors' experience or in any literature which has appeared to date. With use of immediate nephrectomy, combined with routine postoperative irradiation to the operative site, the survival rate (from 1940 through 1947) has been 47% in children of all ages; in babies under 12 mo. of age the survival rate has been 80%. In the effort to raise these rates a study is being made at present of an extended series of patients who are receiving preoperative irradiation, but as yet no conclusive statements can be made for or against this adjunct.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

EXPERIMENTS WITH THE LOCAL ACTION OF OESTROGEN ON THE INTRASPLENIC OVARIAN GRAFT. R. IGLESIAS, A. LIPSCHUTZ, and GUILLERMO ROJAS, Endocrinology **46**:414 (May) 1950.

When estradiol was allowed to act directly on the ovary without being able to reach the general circulation, the behavior of the ovary was fundamentally different from that which was obtained with estrogen reaching the general circulation.

From these comparative findings it is concluded that control of follicular growth and enhanced luteinization induced by estrogen present in the general circulation are not due to a direct action of the hormone on the ovary.

JACOBSEN, Buffalo.

ENDOCRINE INFLUENCES ON IMPLANTATION AND DECIDUOMA FORMATION. B. M. PECKHAM and R. R. GREENE, Endocrinology **46**:489 (May) 1950.

Failure of the rat endometrium to form deciduomas in response to a mechanical stimulus after the seventh day of pregnancy is due to the presence of an inhibitor, probably estrogen, which originates both in the maternal ovaries and in the fetal trophoblast.

JACOBSEN, Buffalo.

THE EFFECT OF CORTISONE ACETATE UPON THE GROWTH OF THE WALKER RAT CARCINOMA AND UPON URINARY NON-PROTEIN NITROGEN, SODIUM CHLORIDE AND POTASSIUM. DWIGHT J. INGLE, MILDRED C. PRESTRUD, and KATHYRN L. RICE, Endocrinology **46**:510 (June) 1950.

The rate of growth of the tumor was definitely suppressed by the administration of cortisone acetate. This result may be without special significance, since the dose of cortisone acetate was sufficiently large to cause a negative nitrogen balance. It may be of greater significance that the tumors were able to remain in an anabolic phase and gain in mass during a time that each animal was in negative nitrogen balance.

JACOBSEN, Buffalo.

INTERFERENCE WITH WOUND HEALING BY THE LOCAL ACTION OF ADRENOCORTICAL STEROIDS. BURTON L. BAKER and WAYNE L. WHITAKER, Endocrinology **46**:544 (June) 1950.

Direct application of hog adrenal extract dissolved in 25% alcohol to cutaneous wounds in the rat caused some delay in closure of the wounds. A striking interference in formation of granulation tissue resulted from this treatment.

JACOBSEN, Buffalo.

THE PRODUCTION OF PERMANENT DIABETES BY HIGHLY PURIFIED GROWTH HORMONE. JAMES CAMPBELL, I. W. F. DAVIDSON, and H. P. LEI, Endocrinology **46**:588 (June) 1950.

Permanent diabetes in dogs has been produced by administration of highly purified growth hormone.

JACOBSEN, Buffalo.

THE GLYCOSTATIC ACTION OF PURIFIED GROWTH HORMONE. JANE A. RUSSELL and ALFRED E. WILHELMI, Endocrinology **47**:26 (July) 1950.

When food is withheld from hypophysectomized rats, the carbohydrate stores of the body become depleted more rapidly than in normal rats. The liver glycogen and blood glucose begin to fall within a few hours, and later the glycogen content of muscle (gastrocnemius) declines to levels well below those seen in normal rats even after prolonged fasting.

Highly purified pituitary growth hormone has been found to maintain normal concentrations of muscle glycogen in fasting hypophysectomized rats.

JACOBSEN, Buffalo.

SOME EFFECTS OF THE HYPOPHYSIS ON IODINE METABOLISM BY THE THYROID GLAND OF THE RAT. W. P. VANDERLAAN and MONTE A. GREER, Endocrinology **47**:36 (July) 1950.

Data are presented which indicate that the thyroid gland of the hypophysectomized rat binds little iodine to protein; this function is restored when thyrotropin is injected subcutaneously.

JACOBSEN, Buffalo.

THE EFFECTS OF HYPOPHYSECTOMY, ADRENALECTOMY AND OF ACTH ADMINISTRATION ON THE PHOSPHORUS METABOLISM OF RATS. CARL A. GENZELL and LEO T. SAMUELS, Endocrinology **47**:48 (July) 1950.

It is concluded that the systems involved in the transfer of phosphate across cell boundaries are under the control of corticotrophin (ACTH); whether this is direct or via the adrenals is not clear. The regulation of the plasma phosphate level, however, depends on some other pituitary factor, probably the growth hormone.

JACOBSEN, Buffalo.

FEMALE PSEUDOHERMAPHRODITISM DUE TO CONGENITAL ADRENAL CORTICAL HYPERPLASIA WITH ASSOCIATED ADDISONIAN-LIKE SYMPTOMS. MILTON M. MAZURSKY and EDWARD SAWAN, J. Pediat. **36**:789 (June) 1950.

Mazursky and Sawan report an infant girl with dehydrated, dusky, cold skin and a very enlarged clitoris. She was first seen at the age of 7 weeks because of failure to gain weight despite adequate food intake. Laboratory studies showed low blood levels for sodium and chloride and increased urinary excretion of 17-ketosteroids. Blood sugar levels were normal. She has been supported successfully with desoxycorticosterone acetate given intramuscularly and added sodium chloride in the diet.

MACDONALD, Pittsburgh.

Diseases of Muscles, Bones, Joints and Lymph Nodes

TREATMENT OF CHRONIC OSTEOMYELITIS WITH PENICILLIN AND PRIMARY CLOSURE OF OPERATIVE WOUNDS. LOUIS G. HOWARD, DONALD G. ANDERSON, KENNETH CHRISTOPHE, THEODORE A. POTTER, and ROBERT L. MOORE, Arch. Surg. **60**:112 (Jan.) 1950.

Based upon the end results obtained in from one to six years, a report is presented of 32 patients with osteomyelitis who were treated with penicillin only and 55 patients with a similar condition who were given penicillin along with surgical intervention and primary closure of operative wounds. Among the 32 treated with penicillin, one died. In five other patients the wound never healed. In 26 patients healing occurred, and of these, 15 had a reslapse after healing. Only 11 of the 32 patients remained healed with systemic administration of penicillin only. Results of treatment with penicillin and operation or with streptomycin and operation in the group of 55 patients with chronic osteomyelitis were more favorable. There was only one failure among this group. The combined treatment is recommended for chronic osteomyelitis.

KAISER, Rochester, N. Y.

MULTIPLE FRACTURES ASSOCIATED WITH SUBDURAL HEMATOMA IN INFANCY. EDWARD F. LIS and GEORGE S. FRAUENBERGER, Pediatrics **6**:890 (Dec.) 1950.

The case report of an infant with subdural hematoma associated with multiple fractures was presented. The etiology was not established.

FROM THE AUTHORS' SUMMARY.

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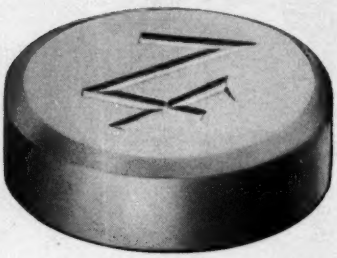

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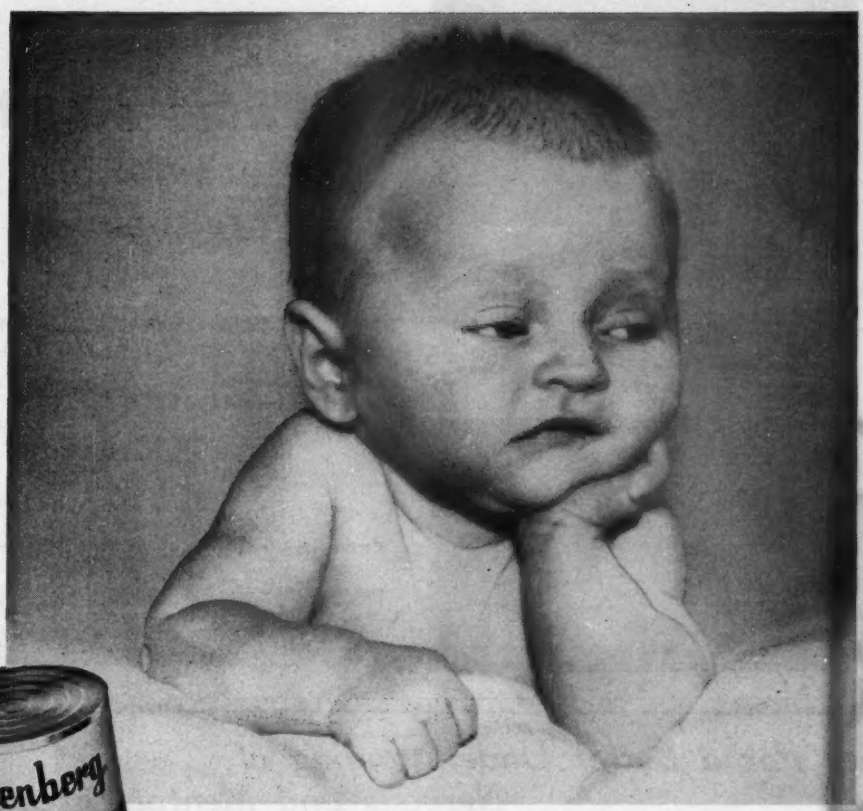

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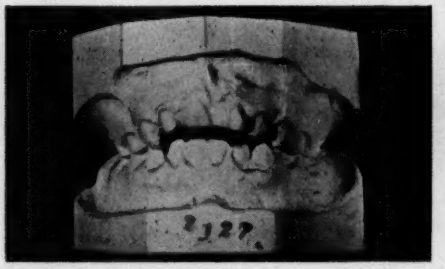

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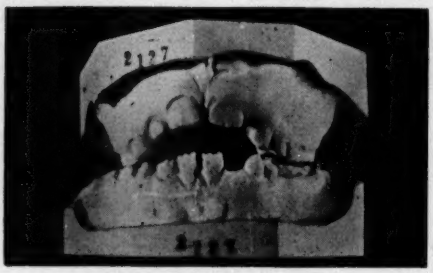

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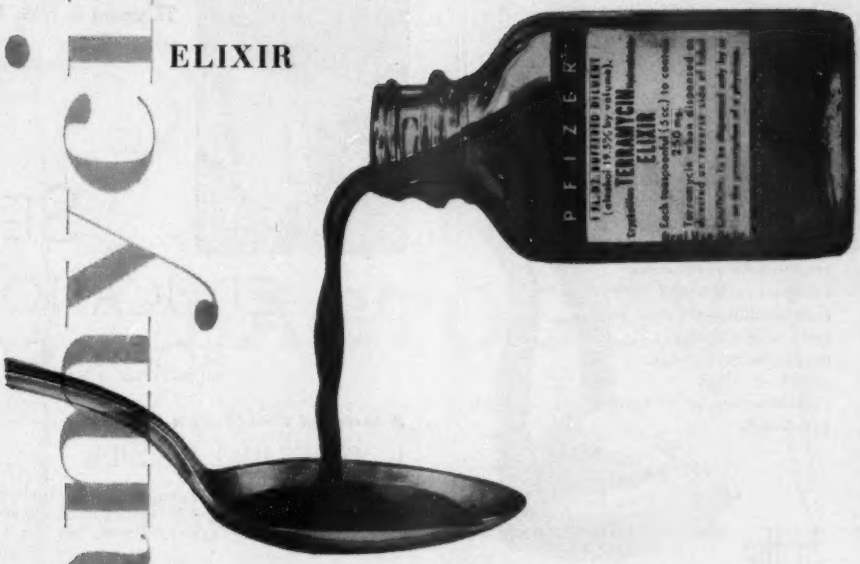

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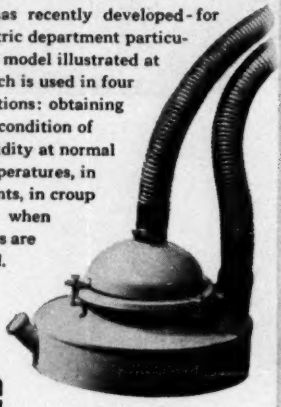

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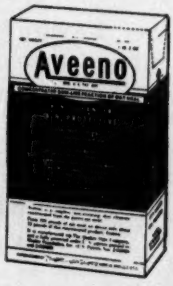

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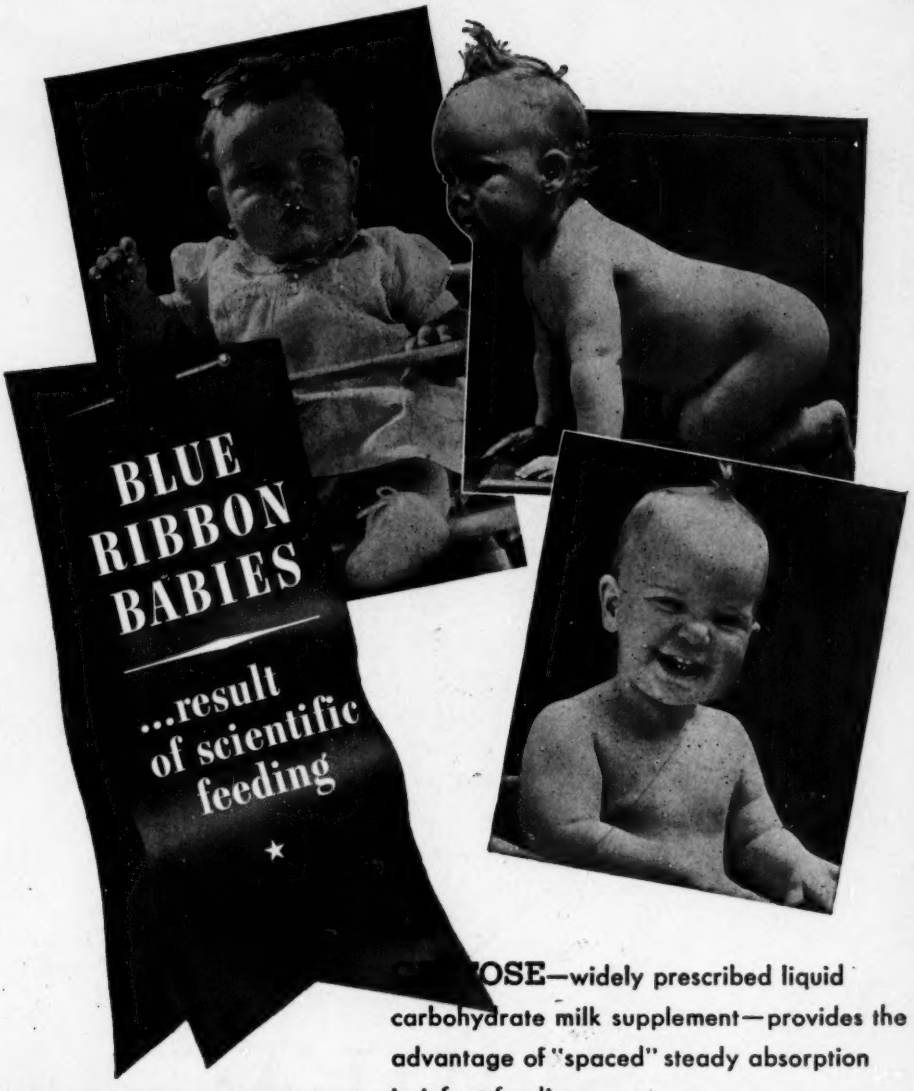

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